1: *Hum Reprod* 1999 Jun;14(6):1534-9 Related Articles, Books, LinkOut

Seminal transforming growth factor-beta in normal and infertile men.

Loras B, Vetele F, El Malki A, Rollet J, Soufir JC, Benahmed M

Institut National de la Sante et de la Recherche Medicale, INSERM U407, Faculte de Medecine Lyon-Sud, B.P. 12, F-69961 Oullins cedex, France.

Transforming growth factor-beta (TGFbeta) is a cytokine with autocrine and paracrine action in the testis and potent immunoregulatory and anti-inflammatory activities. In the present study, we examined the concentration of latent (acid-activatable) and free (active) TGFbeta in seminal plasma from normal subjects (n = 23) and infertile (n = 40) patients, by using a TGFbeta specific immunoenzymological assay, and a bioassay (CCL64 cell line growth inhibition) detecting any form of TGFbeta. Free TGFbeta1 was present in normal subjects at a concentration (1.82 +/- 1.06 ng/ml) close to that known to give maximal stimulation in vitro. In pathological groups, the mean concentrations were not significantly different from the normal ones. Latent TGFbeta1 was present in normal seminal plasma at a high concentration (92.4 +/- 29.2 ng/ml). In subjects with pathologies of both testis and genital apparatus, or with epididymal occlusion, mean latent TGFbeta1 concentrations were normal, whereas transferrin concentrations were lower. The concentrations found in the epididymal occlusion group indicate that TGFbeta1 is, for a large part, secreted by the genital tract. In the testicular pathology group, TGFbeta1 concentrations were 130.7 +/- 61.2 ng/ml, a mean not statistically different from normal, although higher. No differences were found between patients with high and normal blood plasma follicle stimulating hormone, and this is consistent with the notion that most TGFbeta1 in seminal plasma is not of testicular origin. The TGFbeta bioassay ensured that immunologically detected TGFbeta was present in a bioactive or bioactivatable form. Furthermore, the values found in normal and pathological seminal plasmas were usually higher than those detected by the immunoassay, suggesting that other forms of TGFbeta might be present. Together, the present data show that very large amounts of TGFbeta are present in human seminal plasma. The TGFbeta ligand assay in the seminal plasma appears to indicate no differences between normal and infertile subjects.

PMID: 10357971

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1: *Am J Reprod Immunol* 1996 Sep;36(3):157-66 Related Articles, Books, LinkOut

Cytokines of the human reproductive tract.

Srivastava MD, Lippes J, Srivastava BI

Department of Gynecology and Obstetrics, School of Medicine, State University of New York at Buffalo, USA.

PROBLEM: How is it possible that the female genital tract immunologically does not reject spermatooa not the preimplantation and nidating embryo? METHODS: Four fluids of the human reproductive tract, i.e., human oviductal fluid (hOF), follicular fluid (FF), amniotic fluid (AF), and seminal plasma (SP) were investigated by specific ELISA for 18 cytokines. The concentrations, presence or absence of these compounds were evaluated for their possible role in the immunology of the reproductive process. RESULTS: Stem cell factor and IL-11 were detected in all reproductive tract fluids examined whereas large amounts of IL-1 beta and IL-1RA was found in AF and hOF. Follicular fluid revealed IL-2. HOF contained IL 2, IL-6, IL-8, TNF-alpha, MIP-1 alpha, IFN-gamma, and high levels of IL-1 beta, IL-10, IL-1RA, and sIL-2R. Amniotic fluid contained sIL-2R, IL-8, IL-1 beta, IL-1RA, IL-6, TNF-alpha, and MIP-1 alpha. No IL-12 or IL-13 was detected in hOF follicular fluid or amniotic fluid. Almost no free TGF-beta 1 or TGF-beta 2 was found in any reproductive tract fluid except seminal plasma. Seminal plasma contained large quantities of free TGF-beta 1 (9,220 +/- 3,635 pg/mL) in addition to large quantities of latent TGF-beta 2 (2,933 +/- 2,169 pg/mL) and TGF-beta 1 (71,000 +/- 3,240 pg/mL). Furthermore, considerable concentrations of IL-8 (1900 +/- 374 pg/mL) and sIL-2R (350 mu/mL) exist in seminal plasma. CONCLUSIONS: HOF contains a high level of IL-10 (588 +/- 304 pg/mL), a powerful immune suppressor which probably plays a role in regulating immune responses in the fallopian tube and possibly in the endometrial cavity. Our observations suggest that seminal plasma with its huge content of TGF beta provides immune protection for sperm. Unfortunately, such high concentrations of TGF beta may also inhibit an immune defense in any organ in which semen is deposited.

PMID: 8874712

1: *Endocrinology* 1999 Jun;140(6):2480-5 Related Articles, Books

A comparative study on transforming growth factor-beta and activin A for preantral follicles from adult, immature, and diethylstilbestrol-primed immature mice.

Liu X, Andoh K, Abe Y, Kobayashi J, Yamada K, Mizunuma H, Ibuki Y

Department of Obstetrics and Gynecology, Gunma University School of Medicine, Maebashi, Japan.

Both transformation growth factor-beta (TGFbeta) and activin belong to the TGFbeta superfamily, and each receptor is structurally related. We have shown that the action of activin A on folliculogenesis is different in immature and adult mice, so it is of interest to study whether TGFbeta has such an action on follicular development. The effect of TGFbeta on folliculogenesis was studied in isolated preantral follicles from immature, adult, and diethylstilbestrol (DES)-primed immature mice and was compared with that of activin A. TGFbeta caused a significant increase in follicular diameter and estradiol and immunoreactive inhibin secretion in adult mice in a dose-related manner, but did not affect the size of preantral follicles from immature mice. Activin A, on the other hand, caused a significant increase in the size of follicles from immature mice, but did not change the size of preantral follicles from adult mice. TGFbeta enhanced the effect of FSH, whereas activin A completely blocked the action of FSH on preantral follicles from adult mice. Such a specific action of TGFbeta and activin A was age dependent because preantral follicles obtained from 28-day-old mice, compared with those from 11- and 56-day-old mice, showed an intermediate reaction to TGFbeta and activin A. DES pretreatment of 11- and 28-day-old mice caused an enhanced response to FSH, but this response was completely inhibited by TGFbeta. These results indicate that both TGFbeta and activin A have proliferative action and cytodifferentiative action on granulosa cells, but the action of each is age dependent and opposite in direction. In conclusion, although both TGFbeta and activin A belong to the same family, and each receptor is structurally related, both share a specific role in early folliculogenesis before and after puberty.

PMID: 10342832, UI: 99272260

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1: *Steroids* 2000 Oct-Nov;65(10-11):783-94 Related Articles, Books, LinkOut

Endometrial contraception: modulation of molecular determinants of uterine receptivity.

Puri CP, Katkam RR, Sachdeva G, Patil V, Manjramkar DD, Kholkute SD

Institute for Research in Reproduction (Indian Council of Medical Research), Jehangir Merwanji Street, Parel, 400 012, Mumbai, India.

[Medline record in process]

Modulation of endometrial receptivity is a promising approach for fertility regulation since it allows a contraceptive to act specifically at the endometrium. This was corroborated by our previous observations that treatment with low doses of a pure progesterone antagonist (PA, antiprogestin), onapristone (ZK 98299), in bonnet monkeys inhibited fertility by selectively retarding endometrial development, without affecting the hypophyseal-hypothalamic function. In the present study, further investigations, undertaken to analyze the molecular repertoire of a nonreceptive primate endometrium, determined expression of: steroid hormone receptors, i.e. progesterone receptor (PR) and estrogen receptor (ER); cytokines, i.e. leukemia inhibitory factor (LIF): transforming growth factor beta (TGFbeta) and its receptor (TGFbetaR); and cell adhesion molecules, i.e. integrins (alpha(v)beta(3), alpha(1)beta(1)). These studies were conducted during the different phases of the normal menstrual cycle and following treatment with different doses of onapristone (2.5 mg, 5 mg, or 10 mg every third day for one cycle) in bonnet monkeys. The molecules were analysed collectively to explore the possibility of a correlation between expression of these markers and endometrial receptivity and to investigate whether there exists a regulatory link between expression of these molecules under in vivo conditions. Three types of expression patterns of endometrial factors were observed during the peri-implantation period following onapristone treatment: 1) LIF, alpha(v)beta(3), and alpha(1)beta(1) showed significant ($P < 0.02$) down regulation in glandular epithelium of endometria in animals treated with all three doses of onapristone as compared to the control group. This was indicative of their critical role in the progesterone-driven cascade leading to implantation. 2) PR, TGFbeta, and TGFbetaR remained unaffected in the endometria from 2.5 mg treated animals and showed down regulation in animals treated with 5 and 10 mg onapristone as compared to the control group, thereby suggesting that the expression of these

markers may not truely reflect endometrial receptivity per se. However, their facilitatory role in preparing the endometrium for implantation can not be ruled out since continued perturbation in the expression of these molecules may affect endometrial growth, remodelling, and differentiation, which in turn may render the endometrium nonreceptive; 3) ER remained unaltered in endometria of animals rendered infertile with 2.5, 5, and 10 mg onapristone. This observation indirectly suggests that onapristone-induced endometrial changes are mediated via some specific mechanisms. The present study clearly demonstrates that endometrial non-receptivity induced at low doses of onapristone is associated with changes in the expression pattern of specific molecular markers. However, no direct correlation was observed between in vivo expression of TGFbeta, LIF, and integrins, thereby lending support to the concept that there exists redundancy or multiple pathways which regulate implantation events.

PMID: 11108889, UI: 20562921

1: *Mol Cell Endocrinol* 2000 Jan 25;159(1-2):1-5 Related Articles, Books

Oocyte-expressed TGF-beta superfamily members in female fertility.

Elvin JA, Yan C, Matzuk MM

Department of Pathology, Baylor College of Medicine, Houston, TX 77030, USA.

Folliculogenesis is regulated by the interplay of extraovarian and intraovarian factors, and the importance of each type of regulation varies depending on the developmental stage of the follicle. Preantral follicle development is regulated predominantly by factors produced locally within the ovary and within the follicle itself. The oocyte has been shown to produce soluble factor(s), which regulate a number of processes in follicular development, including cumulus expansion in the periovulatory period. Members of the TGFbeta superfamily are potent regulators of cell proliferation and differentiation in a number of organ systems, and three members, growth differentiation factor 9 (GDF-9), bone morphogenetic protein 15 (BMP-15) and BMP-6 are expressed by the oocyte and may mediate effects attributed to the oocyte. Based on knockout mouse models BMP-6 does not play an essential role in ovarian function, but GDF-9 is absolutely required for preantral follicle development. GDF-9 also alters the periovulatory expression of granulosa cell genes and stimulates cumulus expansion. Although BMP-15 is expressed identically to GDF-9, its role in regulating ovarian function is still unknown. This review examines the similarities and differences in sequence, expression, and function of the oocyte-expressed TGFbeta family members with respect to regulating folliculogenesis.

Publication Types:
- Review
- Review, tutorial

PMID: 10687846, UI: 20150554

1: *Mol Hum Reprod* 2000 Jun;6(6):498-503 Related Articles, Books, LinkOut

TGFbeta receptor types I and II and the substrate proteins Smad 2 and 3 are present in human oocytes.

Osterlund C, Fried G

Reproductive Medical Center, Department of Women and Child Health, Karolinska Hospital, S-171 76 Stockholm, Sweden.

We have recently found that values of the transforming growth factor (TGF)beta1 in human ovarian follicular fluid obtained during ovarian stimulation for IVF were higher in women who subsequently became pregnant following embryo transfer. We therefore postulated that TGFbeta1 may have a beneficial effect on the preimplantation embryo and improve the chances of a successful implantation. We have used reverse transcription-polymerase chain reaction (RT-PCR) and immunohistochemistry to investigate the presence in human oocytes and preimplantation embryos of the essential components of the TGFbeta signalling pathway, TGFbeta receptors type I and II and the substrate proteins Smad 2 and 3. We found that both receptors, as well as Smad 2 and 3, were present in the unfertilized oocyte, whereas only the type I receptor and Smad 2 and 3 were present at the blastocyst stage. At the 4-cell and 8-cell stages neither of the receptors was present, but Smad 2 and 3 were present at both stages. These findings support our hypothesis that the TGFbeta1 in follicular fluid may interact with the oocyte and preimplantation embryo via TGFbeta receptors, and that TGFbeta signalling may be important for the development of the oocyte and the preimplantation embryo.

PMID: 10825365

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1: *Theriogenology* 1998 Oct 15;50(6):931-44 Related Articles, Books

Immunohistochemical localization of epidermal growth factor, transforming growth factor-alpha and growth factor-beta s in the caprine peri-implantation period.

Flores JM, Sanchez MA, Garcia P, Sanchez B, Nieto A

Department of Animal Pathology II, Veterinary School Complutense University, Madrid, Spain.

Control over the action of steroid hormones in the uterus and conceptus during the initial period of gestation appears to be regulated locally by growth factors. This study involved immunohistochemical detection of epidermal growth factor (EGF), transforming growth factor-alpha (TGF-alpha) and transforming growth factor-beta s (TGF-beta s), to determine their role in the caprine peri-implantation period. Epidermal growth factor was expressed in the luminal and glandular endometrial epithelium of goats on all days studied (Days 22 to 30 post coitum), but it was not detected in trophoblastic cells or in other embryonic structures. Between Days 22 and 30 post coitum, TGF-alpha was detected in the epithelial cells and superficial stroma of the uterus and in the trophoendodermic cells of the embryo. Transforming growth factor-beta s expression, observed in the endometrium, embryo and extraembryonic membranes on Day 22 post coitum, decreased by Day 24 post coitum and disappeared in the embryo by Day 30 post coitum, while remaining in the other structures. The presence of these growth factors during the peri-implantation period in the goat suggests their participation in proliferation and differentiation phenomena which occur during implantation and embryonic development.

PMID: 10734465

1: *Mol Reprod Dev* 1999 Apr;52(4):341-9 Related Articles, Books, LinkOut

Strain dependency of TGFbeta1 function during embryogenesis.

Kallapur S, Ormsby I, Doetschman T

Division of Neonatology and Pulmonary Biology, Children's Hospital Medical Center, University of Cincinnati, Ohio 45229, USA. kalls0@chmcc.org

There is incomplete penetrance to Tgfb1 knockout phenotypes. About 50% of Tgfb1 homozygous mutant (Tgfb1-/-) and 25% of Tgfb1 heterozygous (Tgfb1+/-) embryos die during embryogenesis. In a mixed NIH/Ola x C57BL/6J/Ola x 129 background partial embryonic lethality of the Tgfb1-/-embryos occurs due to defective yolk sac vasculopoiesis and/or hematopoiesis. We show here that on a predominantly CF-1 genetic background, lack of TGFbeta1 causes a pre-morula lethality in about 50% of the null embryos. This partial lethality is not reversed by transfer of Tgfb1-/- embryos to Tgfb1-/+ hosts. The extent of embryonic lethality in Tgfb1-/- embryos ranges in a background dependent manner from 20% to 100%. Based on these and other studies it is clear that TGFbeta1 acts at two distinct phases of embryogenesis: pre-implantation development and yolk sac vasculogenesis/hematopoiesis. The susceptibility for the pre-implantation lethality depends on a small number of genetic modifiers since a small number of backcrosses onto the high susceptibility strain C57BL/6 leads to complete penetrance of the lethality.

PMID: 10092113

1: *Nat Genet* 1997 Feb;15(2):207-11 Related Articles, Books, LinkOut

Mapping of a major genetic modifier of embryonic lethality in TGF beta 1 knockout mice.

Bonyadi M, Rusholme SA, Cousins FM, Su HC, Biron CA, Farrall M, Akhurst RJ

Department of Medical Genetics, Glasgow University, Duncan Guthrie Institute, Yorkhill, UK.

The transforming growth factor beta 1 (TGF beta 1) signalling pathway is important in embryogenesis and has been implicated in hereditary haemorrhagic telangiectasia (HHT), atherosclerosis, tumorigenesis and immunomodulation. Therefore, identification of factors which modulate TGF beta 1 bioactivity in vivo is important. On a mixed genetic background, approximately 50% Tgfb1-/- conceptuses die midgestation from defective yolk sac vasculogenesis. The other half are developmentally normal but die three weeks postpartum. Intriguingly, the vascular defects of Tgfb1-/- mice share histological similarities to lesions seen in HHT patients. It has been suggested that dichotomy in Tgfb1-/- lethal phenotypes is due to maternal TGF beta 1 rescue of some, but not all, Tgfb1-/- embryos12. Here we show that the Tgfb1-/- phenotype depends on the genetic background of the conceptus. In NIH/Ola, C57BL/6J/Ola and F1 conceptuses, Tgfb1-/- lethality can be categorized into three developmental classes. A major codominant modifier gene of embryo lethality was mapped to proximal mouse chromosome 5, using a genome scan for non-mendelian distribution of alleles in Tgfb1-/- neonatal animals which survive prenatal lethality. This gene accounts for around three quarters of the genetic effect between mouse strains and can, in part, explain the distribution of the three lethal phenotypes. This approach, using neonatal DNA samples, is generally applicable to identification of loci that influence the effect of early embryonic lethal mutations, thus furthering knowledge of genetic interactions that occur during early mammalian development in vivo.

PMID: 9020852

1: *Lab Anim Sci* 1999 Apr;49(2):137-43 Related Articles, Books

Interpretation of phenotype in genetically engineered mice.

Doetschman T

Department of Molecular Genetics, Biochemistry and Microbiology, University of Cincinnati College of Medicine, Ohio, USA.

BACKGROUND AND PURPOSE: In mice, genetic engineering involves two general approaches-addition of an exogenous gene, resulting in transgenic mice, and use of knockout mice, which have a targeted mutation of an endogenous gene. The advantages of these approaches is that questions can be asked about the function of a particular gene in a living mammalian organism, taking into account interactions among cells, tissues, and organs under normal, disease, injury, and stress situations. METHODS: Review of the literature concentrating principally on knockout mice and questions of unexpected phenotypes, lack of phenotype, redundancy, and effect of genetic background on phenotype will be discussed. CONCLUSION: There is little gene redundancy in mammals; knockout phenotypes exist even if none are immediately apparent; and investigating phenotypes in colonies of mixed genetic background may reveal not only more phenotypes, but also may lead to better understanding of the molecular or cellular mechanism underlying the phenotype and to discovery of modifier gene(s).

Publication Types:
- Review
- Review, tutorial

Comment in:
- Lab Anim Sci. 1999 Apr;49(2):134

PMID: 10331542

1: *Fertil Steril* 1996 Aug;66(2):316-26 Related Articles, Books

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Antigenic cross-reactivity of human tracheal mucin with human sperm and trophoblasts correlates with the expression of mucin 8 gene messenger ribonucleic acid in reproductive tract tissues.

D'Cruz OJ, Dunn TS, Pichan P, Hass GG, Sachdev GP

University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma.

OBJECTIVE: To test whether autoimmunity to sperm in men with cystic fibrosis (CF) is a result of cross-reactivity between sperm and carbohydrate sequences of the abnormal CF mucins, we investigated the possible epitope sharing between sperm surface antigens and CF mucin antigens using specific monoclonal antibodies (mAbs) directed to purified CF tracheobronchial mucin-1 (HTM-1) and the expression of tracheal mucin 8 gene (MUC8) mRNA in normal male and female reproductive tract tissues by Northern blot analysis. DESIGN: A panel of mAbs directed to HTM-1 subspecies (types I to V) and polyclonal antibodies (pAb) to native and deglycosylated HTM-1 were tested for their ability to agglutinate motile sperm. An indirect immunofluorescence assay was used to detect expression of cross-reactive HTM-1 epitopes on sperm, term placenta (n = 3), and purified trophoblasts (n = 9). Northern blot analysis was used to detect MUC8 messenger RNA (mRNA) in male and female reproductive tract tissues. SETTING: University of Oklahoma Health Sciences Center, a tertiary care referral center. MAIN OUTCOME MEASURES: The demonstration of cross-reactive mucin at the protein and mRNA levels in reproductive tract tissues. RESULTS: Of the five mucin subspecies, type II, IV, and V mucin-specific mAbs (21.3, 33.3, and 54.1) induced head-to-head agglutination of motile sperm; pAb to deglycosylated mucin had no effect. Sperm agglutination mediated by type IV mucin mAb 33.3 was abrogated completely by D-mannose. Within the term placental villi, type II mucin, was localized to fetal endothelium, type IV mucin was localized to syncytiotrophoblast, and type V mucin was localized to cytotrophoblasts. Immunologic studies correlated with the results of Northern blot analysis, which revealed strong MUC8 mRNA expression in the human testis, placenta, endometrium, and cervix and weak or undetectable levels in the human epididymis, seminal vesicle, ovary, fallopian tube, and uterus. CONCLUSIONS: Both male and female reproductive tract tissues synthesize tracheal MUC8 mucin. Monoclonal antibodies specific to human tracheal mucin subtypes induced "immune-type" agglutination of motile sperm. Therefore, expression of cross-reactive MUC8

mucin epitopes in reproductive tract tissues may contribute to the development of low affinity, carbohydrate-specific, agglutinating antisperm antibodies in the genital tract.

PMID: 8690123

1: *Science* 1988 Sep 30;241(4874):1823-5 Related Articles, Books

Developmental expression of PDGF, TGF-alpha, and TGF-beta genes in preimplantation mouse embryos.

Rappolee DA, Brenner CA, Schultz R, Mark D, Werb Z

Laboratory of Radiobiology and Environmental Health, University of California, San Francisco 94143-0750.

Control of growth and differentiation during mammalian embryogenesis may be regulated by growth factors from embryonic or maternal sources. With the use of single-cell messenger RNA phenotyping, the simultaneous expression of growth factor transcripts in single or small numbers of preimplantation mouse embryos was examined. Transcripts for platelet-derived growth factor A chain (PDGF-A), transforming growth factor (TGF)-alpha, and TGF-beta 1, but not for four other growth factors, were found in whole blastocysts. TGF-alpha, TGF-beta 1, and PDGF antigens were detected in blastocysts by immunocytochemistry. Both PDGF-A and TGF-alpha were detected as maternal transcripts in the unfertilized ovulated oocyte, and again in blastocysts. TGF-beta 1 transcripts appeared only after fertilization. The expression of a subset of growth factors in mouse blastocysts suggests a role for these factors in the growth and differentiation of early mammalian embryos.

PMID: 3175624

1: *Endocrinology* 1989 Sep;125(3):1666-72 Related Articles, Books

Activin-A, inhibin and transforming growth factor-beta modulate growth of two gonadal cell lines.

Gonzalez-Manchon C, Vale W

Clayton Foundation Laboratories for Peptide Biology, Salk Institute, La Jolla, California 92037.

The proliferative and differentiating effects of the gonadal hormones inhibin and activin-A were examined on cell lines derived from the ovary and testis. Activin-A was found to inhibit the growth of CHO-K1 (Chinese hamster ovary) cells in culture, with an IC50 of 3 ng/ml. The maximal response (50% inhibition) required 3 days of incubation in the presence of 40 ng/ml activin-A, and the inhibitory effect was accompanied by morphological changes. Inhibin (10 ng/ml) partially blocked the inhibition of growth by activin. Transforming growth factor-beta (TGF beta), which is structurally related to activin and inhibin, was a very potent inhibitor of the proliferation of CHO-K1 cells, with an IC50 of 0.2 ng/ml and a maximal effect (70% inhibition) at 2 ng/ml. The combination of high concentrations of both TGF beta and activin-A did not result in a greater inhibitory effect than that observed with TGF beta alone, suggesting an overlapping step in the mechanism of action for both factors. In contrast to the results with CHO-K1 cells, differential effects of activin-A and TGF beta were observed in R2C (rat Leydig cell testicular tumor) cells. Activin-A had only a slight effect on proliferation over a 4-day incubation, but inhibited progesterone accumulation ina concentration-dependent fashion within 12 h. TGF beta, on the other hand, was a potent inhibitor of both growth and steroidogenesis in R2C cells. These studies suggest that activin-A and inhibin may regulate proliferation as well as functions of gonadal cells.

PMID: 2759039

1: *J Endocrinol* 1997 Apr;153(1):169-78 Related Articles, Books, LinkOut

Induction of apoptosis in rat thecal/interstitial cells by transforming growth factor alpha plus transforming growth factor beta in vitro.

Foghi A, Teerds KJ, van der Donk H, Dorrington J

Banting and Best Department of Medical Research, University of Toronto, Ontario, Canada.

In each estrous cycle dominant follicles are selected from a growing pool to develop to the preovulatory stage and to ovulate. Those follicles that do not ovulate must be eliminated in order to maintain the constant mass and homeostasis of the ovary. Granulosa cells are lost by apoptosis at the onset of follicular atresia, whereas apoptotic thecal cells are identified at later stages of atresia. Since transforming growth factor (TGF) alpha and TGF beta 1 have been implicated in the regulation of thecal cell physiology we have localized these growth factors by immunohistochemistry in sections of ovaries from 25-day-old rats, an age at which the ovary exhibits a wave of atresia of preantral follicles. Thecal cells contained TGF alpha and TGF beta 1 throughout the entire process of follicular atresia. To determine if these growth factors could influence thecal cell death, thecal/interstitial cells were isolated from 25-day-old rats, and maintained in culture with growth factors. Subconfluent cultures treated with TGF alpha or TGF beta 1 alone remained healthy whereas in the presence of both TGF alpha and TGF beta 1 there was light microscopical evidence of rounding up of cells and detachment from the monolayer. Chromatin condensation and internucleosomal fragmentation, characteristic of apoptosis, were observed by nucleic acid staining and fluorescence microscopy of thecal/interstitial cells treated with TGF alpha plus TGF beta 1. Further evidence that these cells were undergoing apoptosis came from DNA analysis and the demonstration of DNA laddering. This response of thecal/interstitial cells to TGF alpha plus TGF beta 1 was density dependent; confluent cultures were protected from the induction of apoptosis under these conditions. We conclude that thecal cells are eliminated from atretic follicles by the active and strictly regulated process of involving the combined actions of TGF alpha and TGF beta 1.

PMID: 9135581

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TNF-α Messenger RNA and Protein Expression in the Uteroplacental Unit of Mice with Pregnancy Loss[1]

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Abstract

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An elevated expression of TNF-α in embryonic microenvironment was found to be associated with postimplantation loss. In this work, we examined the pattern of TNF-α expression at both the mRNA and the protein level as well as the distribution of TNF-α receptor mRNA in the uteroplacental unit of mice with induced (cyclophosphamide-treated) or spontaneous (CBA/J x DBA/2J mouse combination) pregnancy loss. RNase protection analysis demonstrated an increase in TNF-α mRNA expression in the placentae of mice with pregnancy loss compared with that in control mice. TNF-α messages were localized to the uterine epithelium and stroma as well as the giant and spongiotrophoblast cells of the placenta. The intensity of the hybridization signal in placentae of mice with pregnancy loss was substantially higher than that in control mice. The up-regulation of TNF-α mRNA was accompanied by an increase in the expression of TNF-α receptor I mRNA in the same cell populations. The elevation of TNF-α production was also demonstrated at the protein level. Western blot analysis showed an increased level of the 18- and 26-kDa TNF-α protein species in the uteroplacental unit of mice with pregnancy loss. Immunostaining revealed TNF-α-positive leukocytes located in the uterus and placenta. Finally, we found that immunization of mice with cyclophosphamide-induced pregnancy loss while decreasing the resorption rate in these females resulted in a decline in TNF-α expression at the fetomaternal interface. These data clearly suggest an involvement of TNF-α in pathways leading to both spontaneous and induced placental death.

Introduction

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The presence and normal functioning of cytokine networks at the fetomaternal interface may be important for the continued development of pregnancy (1). TNF-α is a multifunctional cytokine that plays a prominent role in immune and host defense responses, stimulates angiogenesis, influences tissue remodeling, promotes apoptosis, and takes part in the regulation of cell proliferation and differentiation (2, 3, 4, 5, 6, 7). It has also been reported to be instrumental in the regulation of reproductive processes (8, 9). TNF-α was demonstrated to be produced by both uterine and placental cells. In humans, TNF-α mRNA and protein have been identified in syncytio- and extravillous cytotrophoblast (10, 11, 12), and biologically active TNF-α was found in the supernatants of placental and decidual tissue (13, 14). In rodents, TNF-α expression was demonstrated in the uterine epithelium, decidua, and trophoblast (15, 16). Also, TNF-α mRNA transcripts have been identified in murine macrophage-like cells residing in the endometrial stroma and in NK-like cells populating the decidua and metrial gland (15, 16, 17). The expression of TNF-α is tightly regulated during mouse gestation (18), reaching its maximum at midgestation and then remaining stable until the end of pregnancy (15).

The role of uterine and placental TNF-α in pregnancy is poorly understood. It has been suggested that TNF-α may regulate the migration and behavior of uterine leukocytes (19, 20) and affect the myometrial contractions during labor (13). Furthermore, maternal TNF-α might influence blastocyst growth and implantation (21, 22) due to regulation of trophoblast growth and differentiation in early embryos (23). Recent studies on knockout mice have demonstrated that TNF-α is required for normal placental growth and function (24). TNF-α binds to one of two distinct cellular receptors, TNF-α receptor I (TNFRI)[3] (p55) and TNFRII (p75) (25), thereby initiating different cellular responses. Transcripts of both receptors have been found in the uterus and placenta of pregnant mice (26).

Abnormal TNF-α production may be associated with pregnancy failure. The TNF-α level was shown to be significantly elevated in the amniotic fluid of women with uterine infections, and its increased production correlates with the incidence of preterm labor (27). Administration of LPS (an inducer of TNF-α production) or TNF-α itself to pregnant mice results in pregnancy loss (28, 29) or embryo growth retardation (30), whereas treatment with anti-TNF-α Abs or soluble receptors reduces the number of resorptions in mice with a high rate of immune-mediated pregnancy loss (31, 32). Furthermore, enhancement of decidual TNF-α production has been suggested to be one of the mechanisms involved in stress-triggered abortions in mice (33). Also, an increased TNF-α level has been demonstrated in supernatants from decidual cell cultures from the resorption-prone CBA/J x DBA/2J mouse compared with that in the nonresorption-prone CBA/J x BALB/c mouse combination (34). In parallel, an elevation in TNF-α was registered at the mRNA level in placentae of CBA/J x DBA/2J mice (35). Cytokine analysis of supernatants from mixed lymphocyte-placental cell cultures has shown a significantly higher production of TNF-α in supernatants from CBA/J x DBA/2J mice compared with those from CBA/J x BALB/c mice (36).

The correlation between an elevated level of TNF-α and pregnancy failure raises the possibility that normalization of TNF-α expression at the fetomaternal interface may be associated with improved reproductive performance in females with pregnancy loss. It has been widely reported that

alloimmunization or nonspecific immune stimulation may protect the fetus and improve reproductive outcome (37, 38). We have demonstrated that such immunization may prevent the embryonic dismorphogenesis induced by extrinsic and intrinsic factors (39, 40). The protective effect of immunization is generally thought to be due to modification of the cytokine milieu in embryonic microenvironment (41).

In this report we present data characterizing the pattern of TNF-α and TNFRI expression at the fetomaternal interface of mice with spontaneous and induced pregnancy loss and possible changes in this pattern induced by maternal immunization to determine whether the protective effect of immunization in females with pregnancy loss is associated with modulation of TNF-α expression.

Materials and Methods

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Animals

Six- to eight-week-old ICR and C57BL/6 mice and Long Evans rats were obtained from the Tel Aviv University breading colonies. CBA/J females and DBA/2J males were obtained from The Jackson Laboratory (Bar Harbor, ME). The animals were maintained on a 14-h light/10-h dark cycle with food and water ad libitum. To obtain pregnancies, females were caged with males overnight, and the presence of a vaginal plug was designated day 1 of pregnancy.

Animal models of pregnancy loss

Two mouse models of induced and spontaneous pregnancy loss were used in this study.

The CBA/J x DBA/2J mouse combination, which is well known for its high level of postimplantation loss, was used as a model of spontaneous abortions (31). Cyclophosphamide (CP)-treated ICR x ICR and CBA/J x C57BL/6 mouse combinations were used as models of induced pregnancy loss.

CP was injected i.p. on the morning of day 12 of pregnancy at 40 mg/kg (in 0.5 ml saline/20 g body weight). Dosage was proportional to weight at the time of treatment (42). CBA/J females mated to DBA/2J males were sacrificed on day 12 of gestation, while CP-treated mice were sacrificed on day 15 or 19 of pregnancy. The numbers of implantation sites, resorptions, and live fetuses were recorded, and the incidence of postimplantation loss was calculated as described previously (42).

Immunization

CBA/J and ICR females were treated with either allogeneic paternal (C57BL/6) or xenogeneic rat splenocytes, respectively, 21 days before mating as described previously (39, 43). Briefly, spleens were aseptically removed and dispersed in RPMI 1640 medium (Biologic Industries, Israel) by pressing them through a stainless steel mesh. The cells were washed, and their viability was assessed by trypan blue staining. Under nembutal anesthesia (40 mg/kg) the uterus was identified and injected with 25 to 30 x 10^6

splenocytes/0.04 ml saline/horn. Mice injected with saline or syngeneic splenocytes served as controls.

Tissue processing

Placentae together with the adjacent uteri were collected from mice with spontaneous resorptions on day 12 and from CP-treated mice on day 15 of pregnancy. The term resorbing placenta refers to a placenta with a pale or visibly destroyed embryo and remnants of extraembryonic tissues but which can still be identified macroscopically as a placenta. The term nonresorbed placenta refers to a macroscopically normal placenta with a live embryo.

For RNase protection and Western blot analysis, placentae and uteri were immediately snap-frozen in liquid nitrogen and stored at -70°C until use. For in situ hybridization or immunohistochemistry techniques, placentae were fixed in 4% paraformaldehyde or in Bouin's solution, respectively, and embedded in paraffin, and 7-μm sections were further used after histologic examination. Only resorbing placentae containing morphologically unaffected regions were chosen for further analysis.

Probe construction

The 709-bp TNF-α and 640-bp TNFRI cDNAs (provided by Prof. D. Wallach, Weizmann Institute of Science, Rehovot, Israel) were subcloned into the *Eco*RI-*Sac*I and *Eco*RI-*Sph*I sites of the pBluescript SK^+ vector (Stratagene, La Jolla, CA), respectively. After linearization with *Sac*I for TNF-α and with *Sph*I for TNFRI cDNA, the DNA template served for generation of digoxigenin-11-UTP-labeled (Boehringer Mannheim, Mannheim, Germany) antisense RNA probes using T7 RNA polymerase (Stratagene). RNA probes for ß-actin (360 bp) and the prokaryotic *neo* gene (760 bp) were synthesized as described above. The lengths of the generated RNA probes were evaluated by comparing their sizes with that of the digoxigenin-labeled DNA m.w. marker VIII (Boehringer Mannheim) in denatured 5% polyacrylamide gel.

RNase protection analysis

Total RNA was extracted from placentae and uteri by the method of Chomzynski and Sacchi (44) using the Tri-Reagent (Molecular Research Center, Cincinnati, OH). The RNA concentration was calculated by spectrophotometry at 260 and 280 nm, and the integrity of the RNA was monitored by electrophoresis in 1% agarose/2.2 M formaldehyde gel. The following procedures are those described in the protocol of the RNase Protection Assay System (Promega, Madison, WI). Briefly, 30 to 50 μg of total RNA were coprecipitated with 30 ng of antisense RNA probe, incubated overnight in 20 μl of hybridization buffer (80% formamide, 1 mM EDTA, 0.2 M sodium acetate, and 40 mM PIPES, pH 6.4) at 45°C, and then digested with 16 U of RNase ONE (Promega) for 1 h at room temperature. Following RNase inactivation, RNA was precipitated and resuspended in gel loading buffer, and protected fragments were resolved by electrophoresis in denatured 5% polyacrylamide/8 M urea gel. The m.w. of specific mRNA was calculated using the digoxigenin-labeled DNA m.w. marker VIII. RNA was transferred to Nytran nylon membranes (Schleicher & Schuell, Dassel, Germany), which were rinsed briefly in 6x SSC (150 mM sodium chloride and 15 mM sodium citrate, pH 7.0) and exposed to UV light for cross-linking of RNA to the filters. Hybridization bands were visualized by incubating the blots in alkaline

phosphatase-conjugated antidigoxigenin Abs at 1/10,000 dilution (Boehringer Mannheim) and the chemiluminescent substrate CSPD (Tropix, Bedford, MA) followed by exposure to x-ray film.

As a negative control, tissue RNA was substituted by yeast tRNA. Equivalency of RNA loading on the gel was controlled by hybridization of the same quantity of tissue RNA with a ß-actin riboprobe. The quantitative character of the RNase protection assay was confirmed by titration of tissue RNA with the labeled riboprobe and generation of a titration curve (data not shown).

Densitometric analysis of films was performed using B.I.S. 202D image densitometric system (Bio-Rad, Richmond, CA), and results were analyzed by TINA software (Raytest, Straubenhard, Germany).

In situ hybridization

Tissue sections were deparaffinized and processed as previously described (45). Briefly, the sections were washed and heated for 30 min at 70°C in 2x SSC, treated with 10 µg/ml proteinase K (IBI, New Haven, CT) for 15 min at 37°C, and fixed in 4% ice-cold paraformaldehyde. Prehybridization was performed for 1 h at 45°C in 50% formamide, 6x SSPE (150 mM sodium chloride, 10 mM sodium phosphate, and 1 mM EDTA, pH 7.4), 5x Denhardt's solution (Sigma, Rehovot, Israel) and 0.5% SDS. The sections were overlaid with 30 µl of hybridization mixture (50% formamide, 5x Denhardt's solution, 10% dextran sulfate, 6x SSPE, and 0.5% SDS) containing 0.5 ng/µl digoxigenin-labeled antisense RNA probe. Hybridization was conducted overnight at 45°C in a humidified chamber. The slides were washed twice for 15 min in 2x SSC, followed by incubation with 20 µg/ml RNase A (Sigma) for 30 min at 37°C. High stringency washes were performed by incubating the slides twice for 15 min at 50°C in 0.1x SSC followed by a 10-min wash in 0.1x SSC at room temperature. The hybridization signal was detected by alkaline phosphatase-conjugated antidigoxigenin Abs followed by incubation in nitro blue tetrazolium/5-bromo-4-chloro-3-indolyl-phosphate color substrate solution (Boehringer Mannheim) containing 1 mM levamisole according to the manufacturer's recommendations. Finally, sections were lightly counterstained with neutral red, and a positive signal was indicated by a deep purple-brown staining.

As a control for hybridization, a nonhomologic RNA probe synthesized from a prokaryotic *neo* cDNA was substituted for the specific probes. Tissue sections pretreated with 100 µg/ml RNase A (Sigma) for 30 min at 37°C before hybridization served as an additional control.

Western blot analysis

Placentae and uteri were homogenized in ice-cold buffer containing 100 mM Tris-HCl (pH 7.4), 200 mM sodium chloride, 2 mM EDTA, 1 mM PMSF, and 2 µg/ml aprotinin. An equal volume of lysing solution (1% desoxycholate, 0.04% Nonidet P-40, and 0.2% SDS) was added then to each sample, and the resulting homogenates were centrifuged for 10 min at 4°C at 10,000 x *g*, aliquoted, and stored at -70°C until use.

Protein concentration was determined by the Bio-Rad protein assay method (Bio-Rad). Samples containing 50 µg of protein were resolved by electrophoresis in a 12% SDS-polyacrylamide gel.

Prestained m.w. standards (Novex, Rockford, IL) and murine rTNF-α (provided by Prof. D. Wallach, Weizmann Institute of Science) were used as markers. Proteins were transferred to nitrocellulose membranes (Schleicher and Schuell), and nonspecific binding sites on blots were blocked by incubation in 5% (w/v) low fat dried milk in buffer containing 50 mM Tris-HCl (pH 7.4), 500 mM sodium chloride, and 0.1% SDS (TBST) for 2.5 h at room temperature. Filters were incubated in polyclonal TNF-α rabbit antiserum (Endogen, Cambridge, MA) at 15 μg/ml TBST for 30 min at 37°C. Nonimmune rabbit serum, used at the same dilution as the primary Ab, served as a negative control. After intensive washing in TBST, the membranes were incubated for 1 h at room temperature with biotinylated goat anti-rabbit IgG (Jackson ImmunoResearch Laboratories, West Grove, PA) at 10 ng/ml, washed again, and incubated with streptavidin-conjugated horseradish peroxidase (Zymed, San Francisco, CA) at 0,5 μg/ml for 45 min at room temperature. After another wash, the membranes were incubated with ECL reagents (Amersham Life Sciences, Arlington Heights, IL) and exposed to x-ray film.

Immunohistochemistry

Tissue sections were deparaffinized, washed briefly in PBS (pH 7.4), and treated with 1.5 mg/ml hyaluronidase (Sigma) in PBS, pH 6.5, for 1 h at 37°C. Ag retrieval was performed by heating the tissue sections in PBS, pH 7.4, for 30 min at 80°C. Endogenous peroxidase activity was inhibited by incubating the sections in 3% hydrogen peroxide. Nonspecific binding sites were blocked by a 20% solution of FCS in PBS/0.05% Tween (PBST) for 30 min at 37°C. Sections were stained with rabbit anti-mouse TNF-α-specific Abs diluted to 1/70 in 10% FCS/PBST. Nonimmune rabbit serum used at the same dilution as the primary Ab served as a negative control. Then, slides were washed in PBS and incubated for 30 min at room temperature with biotinylated goat anti-rabbit IgG, diluted to 1/1000, followed by incubation in streptavidin-conjugated horseradish peroxidase/PBST at 12 μg/ml. Anti-TNF-α Ab-stained cells were visualized by incubating the sections with 0.2 mg/ml diaminobenzidine (Sigma) followed by counterstaining with 0.1% hematoxylin.

Statistical analysis

Each tested sample of total RNA and protein was obtained by combining four or five placentae in a tested litter. To evaluate the results of RNase protection and Western blot analyses statistically, four or five samples obtained from different litters were analyzed and compared by Student's *t* test. The two-tailed level of significance of differences was $\alpha = 0.05$. The reproducibility of RNase protection and Western blot analysis was tested in two experiments using the same samples.

For in situ hybridization analysis and immunostaining, four or five resorbing and/or nonresorbed uteroplacental units collected from four mice were analyzed for each experimental group. To test reproducibility, in situ hybridization and immunostaining experiments were repeated three times. In each experiment, four or five tissue sections of each uteroplacental unit were processed and analyzed by two independent readers. Results characterizing signal intensity were averaged.

Results

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Pregnancy loss in tested animal models

To estimate the level of postimplantation loss, 15 litters were tested in each animal model.

The rate of resorptions in the CBA/J x DBA/2J mouse combination evaluated on day 12 of pregnancy was 30.4%. The level of resorptions in CP-treated ICR mice reached 32. 3% by day 15 of pregnancy and increased dramatically to approximately 80% on day 19 of pregnancy. The level of resorptions in CBA/J females mated to C57BL/6 males and treated with CP was practically identical with that in CP-treated ICR mice.

TNF-α mRNA expression

TNF-α mRNA expression was evaluated using RNase protection analysis. In placentae of control mice, two species of mRNA corresponding to 320 and 283 bp were detected (Fig. 1⊞). The densitometric analysis revealed that in nonresorbed placentae of mice with induced pregnancy loss, the expression of both fragments was 2.4-fold higher than that in placentae of control mice, while in resorbing placentae of these animals this increase was less prominent. A third fragment, corresponding to 363 bp, was detected only in the placentae of CP-treated mice, whether resorbing or nonresorbed, but not in control mice.

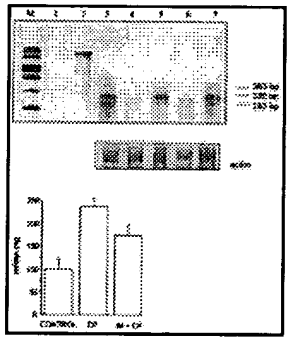

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FIGURE 1. RNase protection analysis of TNF-α mRNA in the placenta of control and CP-treated mice. *Top*, Hybridization with TNF-α-specific antisense RNA probe. *Lane 1*, yeast tRNA, *lane 2*, undigested TNF-α riboprobe, *lane 3*, nonresorbed placenta from CP-treated mice; *lane 4*, placenta from control mice; *lane 5*, resorbing placenta from CP-treated mice; *lane 6*, nonresorbed placenta from immunized mice; *lane 7*, nonresorbed placenta from immunized and CP-treated mice. *Middle*, Hybridization with ß-actin-specific riboprobe (a 250-bp protected fragment). *Bottom*, Densitometric analysis of the protected fragment corresponding to 283 bp. CP, Nonresorbed placentae from CP-treated mice; IM, nonresorbed placentae from immunized mice; IM + CP, nonresorbed placentae from immunized CP-treated mice. Bars represent the percentage of mRNA (±SE) in the experimental groups (CP and IM + CP) relative to the mRNA level in the control group (100%). The level of TNF-α mRNA expression in placentae of CP-treated mice was significantly higher ($p < 0.05$) than that in control mice. Also, TNF-α mRNA expression in placentae from immunized CP-treated mice was significantly lower ($p < 0.05$) than that in placentae of nonimmunized CP-treated mice.

In the CBA/J x DBA/2J mouse model of spontaneous abortions, one fragment of RNA corresponding to 220 bp was detected (Fig. 2⊞). Densitometric analysis revealed a 20% increase in the level of TNF-α mRNA expression in the resorbing vs the nonresorbed placenta.

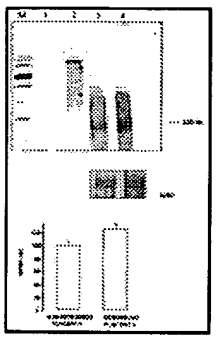

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FIGURE 2. RNase protection analysis of TNF-α mRNA in placentae from CBA/J females (CBA/J x DBA/2J mouse combination). *Top*, Hybridization with TNF-α-specific antisense RNA probe: *lane 1*, yeast tRNA; *lane 2*, undigested TNF-α riboprobe; *lane 3*, nonresorbed placenta; *lane 4*, resorbing placenta. *Middle*, Hybridization with a ß-actin-specific riboprobe (a 250-bp protected fragment). *Bottom*, Densitometric analysis of RNA blots. Bars represent the percentage of mRNA (±SE) in resorbing placentae relative to the mRNA level in nonresorbed placenta (100%). The levels of TNF-α mRNA expression in resorbing and nonresorbed placentae were significantly different ($p < 0.05$).

Localization of TNF-α mRNA

Data from in situ hybridization analysis characterizing the cellular localization and intensity of the hybridization signal are summarized in Table I and Figure 3.

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Table I. Tissue distribution of TNF-α mRNA in the uteroplacental unit[1]

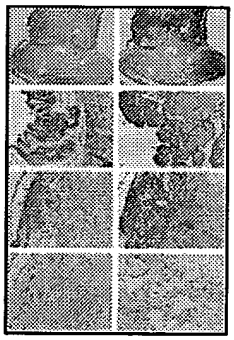

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FIGURE 3. Distribution of TNF-α mRNA in placentae and uteri of control and CP- treated ICR mice (day 15 of pregnancy). *a* and *b*, Low magnification of the uteroplacental unit of control (*a*) and CP-treated (*b*) mice hybridized with TNF-α-specific probes (e, epithelium; m, myometrium; mg, metrial gland; d, decidua; tr, trophoblast; magnification, x15). *c* and *d*, Expression of TNF-α mRNA in the uterine epithelium (arrowheads) of control (*c*) and CP-treated (*d*) mice (x100). *e* and *f*, Expression of TNF-α mRNA in giant (arrowheads) and spongiotrophoblast (sp) cells in the placenta of control (*e*) and CP-treated (*f*) mice (magnification, x100). *g*, Hybridization of placental tissue from control mice with a nonhomologic probe (magnification, x100). *h*, Leukocytes containing TNF-α mRNA (arrowheads) in placental blood lacunae of control mice (magnification, x280).

The distributions of cells expressing TNF-α mRNA in placentae and uteri were similar in control and CP-treated mice. In the uterus, TNF-α mRNA expression was demonstrated in cells of luminal epithelium and stroma (Fig. 3, *c* and *d*, and Table I). In the placenta, giant and spongiotrophoblast were the dominant cell populations containing specific messages (Fig. 3, *e* and *f*), while labyrinthine trophoblast

cells were negative (data not shown). Also, leukocytes containing TNF-α mRNA were detected in placental blood lacunae (Fig. 3*h*).

In the resorbing placenta of CP-treated mice, trophoblast cells demonstrated a loss of TNF-α transcripts, in contrast to metrial gland cells and uterine stroma, which were positive (Table I).

The intensity of the hybridization signal was elevated in the uterine epithelium as well as in trophoblast cells of nonresorbed placentae of CP-treated compared with control mice (Table I and Fig. 3, *a–f*). The resorbing placentae (vs nonresorbed placentae) showed a clear induction of TNF-α mRNA expression in metrial gland cells and an enhanced hybridization signal in uterine stroma. In parallel, the signal was weaker in the uterine epithelium of these placentae (Table I).

The cellular pattern of TNF-α mRNA expression in the uteroplacental unit of the CBA/J x DBA/2J mouse combination was basically similar to that in CP-treated mice, except for metrial gland cells, which demonstrated a positive signal (Table I).

In resorbing placentae of mice with spontaneous pregnancy loss, the specific signal was more intensive than in nonresorbed placentae (Table I). As expected, numerous leukocytes containing TNF-α mRNA were found to infiltrate the tissue areas of the resorbing placenta undergoing necrosis (data not shown).

Hybridization with nonhomologic prokaryotic RNA probe (Fig. 3*g*) as well as hybridization of tissue sections pretreated with RNase before hybridization with specific riboprobes (data not shown) demonstrated no signal.

Localization of TNFRI mRNA

In control mice, the expression of TNFRI mRNA was observed basically in the same cells that expressed TNF-α mRNA (Tables I and II).

In mice with spontaneous and induced abortions, TNFRI mRNA transcripts were found in the uterine epithelium (Table II) as well as in giant and spongiotrophoblast cells (Fig. 4 and Table II). A weak signal was also detected in metrial gland cells of CP-treated mice compared with that in control mice (Table II).

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Table II. Tissue distribution of TNFRI mRNA in the uteroplacental unit[1]

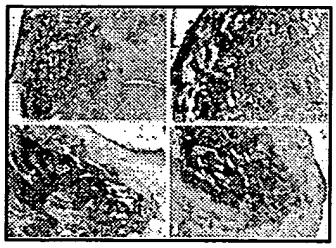

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FIGURE 4. Expression of TNFRI mRNA in control placenta (*a*) and nonresorbed placenta of CP-treated ICR mice (day 15 of pregnancy, *b*) and in nonresorbed (*c*) and resorbing (*d*) placenta of the CBA/J x DBA/2J mouse combination (day 12 of pregnancy). sp, spongiotrophoblast cells. Arrowheads indicate giant trophoblast cells (magnification, x100).

The hybridization signal was more intense in both uteri and placentae of females with CP-induced pregnancy loss than in controls (Fig. 4, *a* and *b*, and Table II).

In the CBA/2 x DBA/2J mouse combination, an elevation of TNFRI mRNA expression was observed in giant trophoblast cells of the resorbing placentae compared with that in the nonresorbed placenta (Table II and Fig. 4, *c* and *d*).

TNF-α protein expression

Results of Western blot analysis of homogenates from placentae of control and CP-treated mice are presented in Figure 5. Probing the blots with TNF-α antiserum revealed multiple immunoreactive proteins with molecular masses of 18, 19, 26, 30, 32, 36, and 38 kDa. These proteins were not detected after incubation of the blots with nonimmune rabbit serum (data not shown).

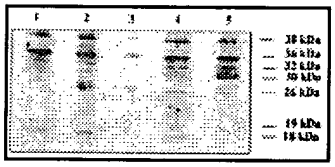

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FIGURE 5. Western blot analysis of TNF-α in placentae of mice treated with CP. Proteins were probed with TNF-α-specific Abs. *Lane 1*, placentae of control mice; *lane 2*, nonresorbed placentae of CP-treated mice; *lanes 3* and *4*, placentae of immunized only or immunized CP-treated mice, respectively; *lane 5*, resorbing placentae of CP-treated mice.

Analysis of TNF-α-immunoreactive proteins showed that the 18- and 26-kDa forms were expressed at a low level in control placentae, while their expression in nonresorbed placentae of animals with pregnancy loss was increased (Fig. 5). The immunoreactive forms corresponding to 30- and 32-kDa TNF-α were highly expressed in resorbing placentae, while their expression in control placentae was weak (Fig. 5). Also, the 18- and 19-kDa immunospecific proteins were not detected in resorbing placentae (Fig. 5).

Immunolocalization of the TNF-α protein

In tissue sections of placentae and uteri of control mice, TNF-α-positive leukocytes were identified in

placental lacunae located between decidua and trophoblast (Fig. 6*b*). A weak positive staining was also detected in placental giant cells, and the intensity of staining was not changed following CP treatment (data not shown).

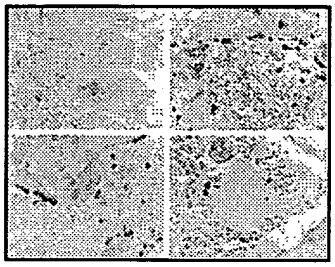

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FIGURE 6. TNF-α-positive leukocytes in placental lacunae of CP-treated ICR mice (day 15 of pregnancy). *a*, Placental tissue sections incubated with nonimmune rabbit antiserum. *b* through *d*, TNF-α-positive leukocytes (arrowheads) in control (*b*), CP-treated (*c*), and immunized CP-treated (*d*) mice. Magnification, x220.

The cellular patterns of TNF-α protein expression in the uteroplacental units of control mice (Fig. 6*b*) and CP-treated mice (Fig. 6*c*) were similar. Also, the distribution of TNF-α-positive cells in the uteroplacental unit of the CBA/J x DBA/2J mouse combination was basically the same as that in CP-treated mice (data not shown). No staining was observed in the tissue sections incubated with nonimmune rabbit serum (Fig. 6*a*).

Effect of immunization on TNF-α expression at the fetomaternal interface

Since our previous works (39, 43) demonstrated that >80% of nonresorbed day 15 placentae in CP-treated mice are destined to be resorbed by the end of pregnancy, we used still nonresorbed 15-day-old placentae from immunized and nonimmunized mice treated with CP to evaluate the effect of immunization on TNF-α expression in the uteroplacental unit.

In immunized CP-treated mice, in situ hybridization analysis revealed a decreased intensity of the hybridization signal in the uterine epithelium and trophoblast cells (Table I).

Results of RNase protection analysis also showed a clear decrease in placental TNF-α mRNA expression following immunization. Thus, the expression of the 283-bp fragment was lower in placentae of immunized CP-treated (Fig. 1, *lane 7*) than in those of nonimmunized CP-treated mice (Fig. 1, *lane 3*).

Finally, immunization resulted in a clear decrease in TNF-α protein expression in the uteroplacental unit of CP-treated mice (Fig. 5). The proportion of leukocytes expressing the TNF-α protein in placentae of mice with pregnancy loss was also decreased following immunization (Fig. 6, *c* and *d*).

No major differences were found in TNFRI mRNA expression in placentae of CP-treated mice following immunization, except for metrial gland cells, which showed a loss of TNFRI mRNA transcripts (Table II).

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It was shown earlier that the pattern of TNF-α expression in combined nonresorbed and resorbing placentae obtained from mice exhibiting a high rate of resorptions differs significantly from that observed in nonresorption-prone mice (35). It might be supposed, however, that resorbing and nonresorbed placentae have different patterns of TNF-α expression. Therefore, in the present work, TNF-α expression was tested separately in nonresorbed and resorbing placentae.

The quantitative analysis of mRNA expression revealed that in mice with CP-induced pregnancy loss, TNF-α mRNA expression was higher in nonresorbed placentae compared with that in control untreated animals. Also, in placentae of mice with CP-induced pregnancy loss, three forms of TNF-α mRNA corresponding to the protected fragments of 363, 320, and 283 bp were revealed, while in placentae of control mice only the 283- and 320-bp TNF-α mRNA forms were detected. The physiologic role of the proteins encoded by these transcripts remains to be elucidated. It cannot be excluded that the 363-bp TNF-α mRNA variant detected in destined to be resorbed placentae may encode a TNF-α form contributing to signals mediating cell death.

In parallel, a substantial increase in the level of TNF-α mRNA expression in resorbing placentae of CBA females mated to DBA/2 males compared with that in nonresorbed placentae of these females was observed. However, unlike ICR mice, in placentae of the CBA/J x DBA/2J mouse combination we detected only a 220-bp TNF-α mRNA variant. This difference may be attributed to the TNF-α gene polymorphism demonstrated in different mouse strains (46). It has been shown that different sensitivities of various mouse strains to infections and some physical factors may be associated with TNF-α gene polymorphism (47, 48, 49). Whether the differences in TNF-α transcripts found in placentae of ICR and CBA mice have some functional significance remains to be elucidated.

An increased expression of TNF-α in placentae of mice with a high rate of pregnancy loss was observed not only at the mRNA but also at the protein level. Western blot analysis of proteins from placentae of mice with induced abortions revealed, besides the earlier described 18-kDa secreted and the 26-kDa membrane forms (50), multiple variants of 26, 30, 32, 36, and 38 kDa of the TNF-α protein. It is possible that the 36- and 38-kDa species are dimers of the 18- and 19-kDa TNF-α forms, respectively. The 30- and 32-kDa immunoreactive forms of TNF-α, were highly expressed in the resorbing placenta of mice with pregnancy loss. Such a finding may suggest that TNF-α gene expression may be differentially regulated at the post-transcriptional and/or post-translational level at different stages of the placental death process. Further studies are needed for understanding the biologic functions of these TNF-α forms.

The uterine epithelium and stroma as well as placental giant and spongiotrophoblast cells were found to express TNF-α mRNA. This cellular pattern of TNF-α mRNA expression is practically identical with that observed in the pioneer works of Hunt et al. performed in nonresorption-prone Swiss and C57BL/6 mice (18, 15). Additionally, as expected, tissue areas in resorbing placentae undergoing necrosis were found to be infiltrated with numerous leukocytes containing the TNF-α mRNA transcripts.

Earlier studies in the CBA/J x DBA/2J mouse combination in which combined nonresorbed and resorbing placentae were tested raised the question of whether the elevation in placental TNF-α expression is an upstream event or, the opposite, a consequence of placental death (35). The results of the present study may clarify this point.

Indeed, our studies revealed an increased expression of TNF-α not only in resorbing placentae of the CBA/J x DBA/2J mouse combination, but also in the nonresorbed placenta of mice with CP-induced pregnancy loss. In this model, the level of resorption reaches ~30% up to day 15 of pregnancy and exceeds 80% by the end of pregnancy. This fact allows us to suppose that most of nonresorbed uteroplacental units tested on day 15 of pregnancy in this model are destined to be resorbed by the end of pregnancy. Thus, the elevation in TNF-α expression demonstrated in nonresorbed placentae of CP-treated mice is an event that precedes placental death.

The involvement of TNF-α in mechanisms underlying pregnancy loss was additionally confirmed by the analysis of its expression in mice with reproductive failure after immunization. It was reported earlier that maternal alloimmunization with BALB/c lymphocytes significantly decreased the level of pregnancy loss in the CBA/J x DBA/2J mouse combination (37). It was also demonstrated that nonspecific maternal immunization with CFA may improve the reproductive performance of CBA/J females mated to DBA/2J males (42). Finally, the level of CP-induced pregnancy loss in CBA/J x C57BL/6 or ICR x ICR mouse models was shown to be decreased by specific maternal immunization with allogeneic paternal splenocytes or nonspecific immunization with rat splenocytes, respectively (39, 43). In this study we have clearly demonstrated that the decrease in the rate of induced resorptions caused by maternal immunization is accompanied by a decline in the TNF-α mRNA level and by a decrease in the levels of all immunoreactive forms of the TNF-α protein at the fetomaternal interface.

Finally, an increased expression of TNFRI mRNA transcripts was demonstrated in placentae and uteri of mice with pregnancy loss. This finding seems to implicate the existence of a TNF-α-associated signaling pathway leading to placental death. Indeed, since the level of TNFRI mRNA in the placenta was constant throughout pregnancy (51), it is reasonable to suppose that its increased expression may lead to an alteration of TNF-α signaling in the placenta. One of the cellular responses to TNF-α is suggested to be associated with apoptotic cell death (6). It has recently been shown that TNF-α may promote apoptosis in trophoblast cells following binding to TNFRI (52). This ligand-receptor interaction was found to be critical, since cells lacking the TNFRI did not show a detectable level of apoptosis (25).

In conclusion, the results of the present study clearly demonstrate that up-regulation of TNF-α expression in the embryonic microenvironment may contribute to spontaneous and induced placental death. Furthermore, down-regulation of TNF-α expression by maternal immunization might play an important role in mechanisms underlying its beneficial effect on reproductive performance.

Acknowledgments

We are grateful to Dr. J. Zaretsky for critical reading of the article and to Prof. D. Wallach for providing us with murine rTNF-α and cDNAs of murine TNF-α and TNFRI. We appreciate the help of Dr. Z. Zaslavsky in performing the densitometric analysis and of Mr. A. Pinchasov for preparation of the photomicrographs.

Footnotes

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[3] Abbreviations used in this paper: TNFRI, TNF-α receptor I; CP, cyclophosphamide.

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Differential regulation of TGF-beta 2 by hormones in rat uterus and mammary gland.

Schneider SL, Gollnick SO, Grande C, Pazik JE, Tomasi TB

Department of Molecular Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA.

Previous work from this laboratory has shown that transforming growth factor beta 2 (TGF-beta 2) mRNA is abundant in the pregnant uterus. In the present study, we examined the synthesis and secretion of TGF-beta 1,2 and 3 in the rat uterus and mammary gland and show differential secretion and expression of TGF-beta 2 in a tissue specific manner. Elevated levels of TGF-beta 2 were detected in late pregnant maternal plasmas (> 100 pM), and in the milk (> 500 pM) during early lactation. High concentrations of TGF-beta 2 (> 200 pM) were also detected in uterine fluids collected from ovariectomized adult rats after high dose estrogen treatment. TGF-beta 2 mRNA levels were elevated in lobuloalveolar epithelial cells isolated from pregnant mammary gland. Three major transcripts of 3.5, 4.0, and 4.7 kb were seen, of which the 4.7 kb, dominates. Mammary glands of estrogen treated ovariectomized rats showed a similar pattern of TGF-beta 2 transcripts. In contrast, four major TGF-beta 2 mRNA transcripts of 5.7, 4.7, 4.0, and 3.5 kb, with the dominant species of 4.0 and 5.7 kb, were observed in uteri from the estrogen treated animals up to 48 h after the last estrogen injection. This suggests that TGF-beta 2 is regulated in a tissue specific manner. We conclude that the secretion of TGF-beta 2 is tightly regulated by hormones and that estrogen and prolactin are critical factors in the tissue-specific regulation of the local production of TGF-beta 2 in the mammary gland and female reproductive tract.

PMID: 9023817

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Transforming growth factor beta in bovine placentas.

Munson L, Wilhite A, Boltz VF, Wilkinson JE

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Transforming growth factor beta s (TGF beta) are a family of multifunctional growth factors that are important embryonic morphogens. Because TGF beta s may regulate the development of epitheliochorial placentas, we investigated the location, expression, secretion, and effects of TGF beta s in bovine placentomes and cell cultures derived from chorionic and endometrial epithelia. Placentomes from early second-trimester pregnancies were examined by immunohistochemistry for TGF beta 1, TGF beta 2, and TGF beta 3, and for TGF beta expression in Northern slot-blots. Effects of TGF beta s were assessed in trophoblastic and endometrial epithelial cell lines by DNA synthesis assays. Secretion of TGF beta s by trophoblastic and endometrial epithelial cells was determined using bioassays. All forms of TGF beta were immunolocalized in bovine placentomes. TGF beta mRNA was expressed in chorioallantois, caruncles, and in cultured trophoblastic and endometrial epithelial cells. Endometrial and trophoblastic cells secreted active and latent TGF beta s, and these cells had a transient proliferative response to all forms of TGF beta. These results indicate that TGF beta s are present at the fetal-maternal interface of the bovine placentome and may promote endometrial and chorionic growth.

PMID: 8879485

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Ovine endometrial expression of transforming growth factor beta isoforms during the peri-implantation period.

Dore JJ, Wilkinson JE, Godkin JD

Department of Animal Science, University of Tennessee, Knoxville 37901, USA.

During the estrous cycle and early pregnancy, the uterus undergoes a variety o morphological changes. Because of their powerful effects on angiogenesis, on extracellular matrix modification, and on cellular proliferation and differentiation, the transforming growth factor beta (TGF beta) family of polypeptides may be involved in the regulation of pregnancy-related endometrial modification. In this study, endometrial stead-state mRNA expression of the three isoforms, TGF beta 1, beta 2, and beta 3, was quantified, and the proteins were localized during the later part of the estrous cycle (Day 13 and 16) and during early pregnancy (Days 13 through 30) in sheep. TGF beta 1 mRNA was expressed as a single transcript with steady-state mRNA expression levels 2-fold higher on Day 16 of the estrous cycle than on Day 13 of the estrous cycle ($p < or = 0.002$) or Days 13 and 16 ($p < or = 0.004$) and 0.008, respectively) of gestation. During pregnancy, levels increased progressively to peak on Day 27 (2.5-fold above Day 16 of pregnancy; $p < or = 0.0001$) and then leveled off at Day 30. Immunocytochemical localization of TGF beta 1 demonstrated protein in glandular protein in glandular and luminal epithelium at all days examined. TGF beta 2 mRNA was expressed as five distinct transcripts, and mRNA expression levels were lowest in Day 16 pregnant endometrium. Thereafter the expression level increased steadily through Day 30 ($p < or = 0.0003$). TGF beta 2 protein was localized in epithelium, diffusely within the endometrial stroma, and in leukocyte-like cells within the stroma. TGF beta 3 was expressed as one major transcripts and two minor transcripts. As with TGF beta 1, there was a dramatic difference in TGF beta 3 levels between Day 16 of pregnancy and Day 16 of the estrous cycle (3.8-fold, $p < or = 0.0001$). In pregnant ewes, endometrial TGF beta 3 levels increased 1.9-fold ($p = 0.13$) between Days 16 and 23 and remained relatively constant through Day 30. Immunohistochemistry localized TGF beta 3 protein most prominantly in the subepithelial stroma of the caruncule from Day 16 of the cycle in endometrial tissue. The observed changes in mRNA and protein expression patterns of TGF beta s within the ovine endometrium suggest that TGF beta s play a role in restructuring and modifying endometrium for a subsequent estrous cycle and/or

pregnancy.

PMID: 8722629

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Differential localization of TGF-beta 2 in mouse preimplantation and early postimplantation development.

Slager HG, Lawson KA, van den Eijnden-van Raaij AJ, de Laat SW, Mummery CL

Hubrecht Laboratory, The Netherlands Institute for Developmental Biology, Utrecht.

The localization of transforming growth factor type beta 2 (TGF-beta 2) has been followed during preimplantation and early postimplantation murine development using an anti-peptide antibody that specifically recognizes TGF-beta 2. The staining pattern showed that TGF-beta 2 is expressed from the four-cell stage onward and is differentially regulated as cells diverge to various lineages. High levels of staining were found in the trophectoderm of the blastocyst but no staining was observed in the inner cell mass. During postimplantation development the primitive and embryonic ectoderm also lacked detectable staining while visceral endoderm stained well. Parietal endoderm cells also showed positive staining reaction although to a lesser extent than visceral endoderm cells. These findings were confirmed in model systems of the embryo, namely, embryonal carcinoma and embryonic stem cells differentiated to to cells with either visceral or parietal endoderm characteristics. The possible regulatory role of this factor in early embryogenesis is discussed.

PMID: 2040369

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Cell type-specific expression of transforming growth factor-beta 1 in the mouse uterus during the periimplantation period.

Tamada H, McMaster MT, Flanders KC, Andrews GK, Dey SK

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Immunohistochemistry and in situ and Northern blot hybridization were employed to determine temporal and spatial expression of transforming growth factor-beta 1 (TGF beta 1) in the mouse uterus during the periimplantation period. The polyclonal antisera anti-LC-(1-30) and anti-CC-(1-30), raised against two different preparations of a peptide corresponding to the amino-terminal 30 amino acids of TGF beta 1, were used for histochemical analyses because of their distinct staining patterns. Anti-LC shows intracellular staining, while staining by anti-CC is primarily extracellular. The colocalization of intracellular staining by anti-LC with in situ hybridization of TGF beta 1 mRNA in the luminal and glandular epithelia on days 1-4 of pregnancy (day 1 = vaginal plug) indicates that the epithelial cells are the primary sites of TGF beta 1 synthesis during the preimplantation period. On the other hand, staining of the extracellular matrix of the stroma by anti-CC during this period suggests an active accumulation of TGF-beta 1 that is synthesized in and secreted from the epithelia. While intracellular staining and accumulation of TGF-beta 1 mRNA in the epithelia were clearly evident on days 1-4, the extracellular staining showed temporal fluctuations. The clear extracellular staining of the stroma that was observed on day 1 was absent on day 2; moderate staining was again visualized in the stroma on day 3 and was markedly increased on day 4.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 2284009

1: *Am J Reprod Immunol* 1997 Jun;37(6):421-6 Related Articles, Books, LinkOut

Maternal response to paternal trophoblast antigens.

Mowbray J, Jalali R, Chaouat G, Clark DA, Underwood J, Allen WR, Mathias S

Imperial College School of Medicine at St. Mary's, London, United Kingdom.

PROBLEM: What is the function of the immunoglobulin (Ig) G antibody bound to trophoblast in normal pregnancy, and what is the antigen? METHOD: IgG was acid eluted from term human placental microvesicles and reacted with the antigen, R80K, left on the vesicles. The eluted antibody was used to detect the antigen on monocytes, lymphocytes, and lymphoblastoid cell lines. The eluted antibody is highly polymorphic, but monoclonal antibodies (mAbs) were made against conserved regions of the molecule. These also reacted with the murine equivalent of the human R80K and were used in inhibition studies of natural killer (NK) cell killing and the mouse abortion models, CBA x DBA2 F1 resorption in CBA females, the endotoxin-induced resorption model, and a sonic stress-induced murine resorption model. RESULTS: All 600 syncytiotrophoblast microvesicle preparations of human term placenta had IgG antibody bound, elutable at pH 3.0. The eluted antibody reacted with about 15% of unrelated human placentae. In horses mares make detectable antibody early in pregnancy, at about the time of implantation. The IgG antibody was bound to an 80-kDa protein (R80K) also detected on B lymphocytes and monocytes. In HLA homozygous lymphoblastoid B cell lines, which reacted with one or more eluted antibodies, had a pattern of cytotoxicity independent of HLA Class I; and as a single 80-kDa peptide chain, R80K did not resemble HLA molecules. Genetic studies in horses show that of the two paternal allotypes of R80K detectable by placental alloantibodies, only one, usually the grandpaternal one, is present in all the placentae of a sibship. Two of 26 eluted human antibodies had affinity for K562 and inhibited killing by human peripheral blood NK cells. One mAb, BA11, against a conserved site on R80K inhibited killing of K562, and also reacted with the murine R80K homologue. BA11 inhibited murine NK cell killing and virtually completely inhibited three NK cell-dependent mouse resorption models. CONCLUSION: R80K protein is a target molecule for NK cell activity expressed on all placentae. It has a polymorphic alloantigenic determinant completely covered with maternal antibody in all successful term pregnancies. In murine NK cell-dependent models of abortion, a mAb against a monomorphic determinant present in human and murine

R80K prevents abortion very effectively. It seems that the R80K molecule must be covered with antibody to prevent NK attacks on trophoblast.

PMID: 9228296

1: *Am J Reprod Immunol* 1996 Jan;35(1):34-42 Related Articles, Books, LinkOut

Immunological prevention of spontaneous early embryo resorption is mediated by non-specific immunosimulation.

Baines MG, Duclos AJ, de Fougerolles AR, Gendron RL

Department of Microbiology and Immunology, McGill University, Montreal, Quebec.

PROBLEM: Spontaneous early embryo resorption following implantation occurs in many species, but little is known regarding the causes or the prevention of early pregnancy failure. Embryo and fetal loss have widely been assumed to be due to maternal allospecific immune rejection. Alloimmunization therapy with paternal tissues has been successfully used in human and murine pregnancies to prevent early embryo demise. The mechanisms of this treatment have been assumed to be the induction of antigen specific, fetal "graft" enhancing antibodies and suppressor cells. The purpose of this study was to investigate the validity of this assumption. METHOD: To investigate these general assumptions, female CBA/J mice were immunized with either specific or nonspecific antigens prior to mating with DBA/2 or Balb/c males. Further, a model system for the study of bacterial lipopolysaccharide (LPS) induced abortion was used to demonstrate the nature of antigen specific immune protection against abortion. RESULTS: Whereas the administration of 1 microgram of LPS to CFW female x CFW male pregnant mice on day 7 of gestation induced complete fetal resorption, prior immunization with 20 micrograms of LPS completely prevented LPS induced abortion as long as the anti-LPS antibody titers remained above a threshold value of about 1/500. Therefore, early embryo loss could be induced by a bacterial infection and could be prevented by appropriate immunity to abortogenic factors. However, due to the short half-life of IgM antibodies, immunity to LPS was short-lived and the protective effect of LPS immunization against LPS induced abortion waned after 5 wk. Through the use of the CBA/J female x DBA/2 male model system to study spontaneous early embryo loss, previous vaccination of CBA/J female mice with Balb/c spleen cells expressing paternal MHC antigens, complete Freund's adjuvant (CFA) or LPS, all decreased the incidence of spontaneous resorption in subsequent pregnancies. Similarly, a previous mating with a Balb/c male prevented spontaneous embryo loss for a period of up to 6 wk. However, none of the immunotherapeutic vaccinations or matings had a permanent effect on CBA/J female x DBA/2 male embryo survival, which one would have expected if specific

immune mediators were involved. CONCLUSION: The results of this study indicated that the decrease in the incidence of spontaneous embryo resorption following alloimmunization was more likely to be due to nonspecific immunomodulatory effects on the immune system of the female mice, as opposed to specific antipaternal immunity. This may, in part, explain the placebo effects observed for alloimmunization therapy for human habitual pregnancy loss. The relevance of these results to the development of immunotherapy strategies for the prevention of habitual abortion is discussed.

PMID: 8789558

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PMID: 10859244

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Kinetics of lymphoproliferative responses of lymphocytes harvested from the uterine draining lymph nodes during pregnancy in rats.
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PMID: 2213723

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1: *J Steroid Biochem Mol Biol* 1994 Jun;49(2-3):107-21

Immunologically mediated abortion (IMA).

Giacomucci E, Bulletti C, Polli V, Prefetto RA, Flamigni C

Department of Obstetrics and Gynecology, University of Bologna, Italy.

Roughly 20% of all clinical pregnancies evolve into "spontaneous abortions". The causes of spontaneous abortion have been determined in under 60% of the total and comprise genetic, infectious, hormonal and immunological factors. In some cases the immune tolerance mechanism may be impaired and the foetus immunologically rejected (IMA, immunologically mediated abortion). The immunological mechanism implicated depends on the time in which pregnancy loss takes place. During preimplantation and up to the end of implantation (13th day) the cell-mediated immune mechanism (potential alloimmune etiologies) is responsible for early abortion. This mechanism involves immunocompetent decidual cells (eGL, endometrial granulated lymphocytes) already present during pre-decidualization (late luteal phase) and their production of soluble factors or cytokines. Once the implantation process is over, after blastocyst penetration of the stroma and the decidual reaction of uterine tissue, IMA could be caused by cell-mediated and humoral mechanism (anti-paternal cytotoxic antibodies or autoantibody etiology), by the production of paternal anti major histocompatibility complex antibodies, or even by an autoimmune disorder leading to the production of autoantibodies (antiphospholipid antibodies, antinuclear antibodies or polyclonal B cell activation). The diagnostic work-up adopted to select IMA patients is crucial and includes primary (karyotype of both partners, toxo-test, hysterosalpingography, endometrial biopsy, thyroid function tests, serum hprolactin, luteal phase dating) and secondary (full hemochromocytometric test, search for LE cells, lupus anticoagulant, anticardiolipin, antinuclear antibodies, Rheumatoid factor, blood complement VDRL) investigations. Therapeutical approaches vary. If autoimmune disorders are demonstrated therapies with different combinations of corticosteroids, aspirin and heparin or intravenous immunoglobulin are administered. Otherwise, therapy with paternal or donor peripheral blood mononuclear cells should be instituted.

Publication Types:
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- Review, tutorial

PMID: 8031707

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Immunoregulatory molecules of trophoblast and decidual suppressor cell origin at the maternofetal interface.

Clark DA, Slapsys R, Chaput A, Walker C, Brierley J, Daya S, Rosenthal KL

The mammalian fetus expresses a variety of paternal histocompatible, oncofetal, and trophoblast antigens against which the mother can mount an immune response. Survival of the "fetal graft" appears to depend upon local immunosuppressive mechanisms in lymph nodes draining the uterus and at the intrauterine implanation site itself. Nonspecific not-T-Fc-receptor-bearing small lymphocytes containing cytoplasmic granules present in successfully allopregnant mice can suppress both the generation of maternal-antipaternal killer T cells and the infiltration of cytotoxic T lymphocytes into sponge-matrix allografts during the effector phase of the immune response. These suppressor cells are deficient at the implantation sites of xenogeneic and allogeneic mouse embryos that are susceptible to maternal immunity and are destined to resorb. A soluble suppressor factor of approximately 100,000 daltons in size can be obtained from the suppressor cells and acts to block the response of T cells to interleukin-2 by interfering with IL-2 receptors. The development of the suppressor cells in the decidua requires certain hormonal signals as well as signals provided by trophoblast cells. Freshly explanted or cultured murine trophoblast cell lines elaborate soluble factor(s) that are active in recruitment or activation of suppressor cells. Since suppressor cells may be isolated from decidua of successfully allopregnant humans, the suppressor cell mechanism and its regulation may represent a key factor in the protection of the "fetal allograft" from rejection by maternal immunity.

PMID: 2940880

1: *Int J Fertil* 1975;20(3):137-40 Related Articles, Books

The presence of paternal H-2 antigens on hybrid mouse blastocysts during experimental delay of implantation and the disappearance of these antigens after onset of implantation.

Hakansson S, Heyner S, Sundqvist KG, Bergstrom S

The presence of paternal H-2 antigens on hybrid mouse blastocysts before and during implantation was investigated by means of the isotope anti-globulin technique. It was found that experimentally delayed blastocysts possess paternal H-2 antigens whereas these antigens can no longer be detected 14 hours after estradiol activation of delayed blastocysts.

PMID: 4392

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=> s TGF beta

L1 68514 TGF BETA

=> s l1 and 2

L2 27819 L1 AND 2

=> s l2 and sperm antigen

L3 1 L2 AND SPERM ANTIGEN

=> d l3 all

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
AN 1998:618828 CAPLUS
DN 129:212101
TI Treatment and diagnosis of infertility using **TGF.beta.** or activin
IN Robertson, Sarah Anne; Tremellen, Kelton Paul
PA Luminis Pty. Ltd., Australia
SO PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-18
ICS A61K039-00; G01N033-68
CC 2-3 (Mammalian Hormones)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9839021	A1	19980911	WO 1998-AU149	19980306

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AU 9862846	A1	19980922	AU 1998-62846	19980306
AU 722150	B2	20000720		
EP 1028743	A1	20000823	EP 1998-906749	19980306

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRAI AU 1997-5508 19970306
WO 1998-AU149 19980306

AB A method of treating an infertility condition in humans or mammals, by exposure of a prospective mother to **TGF.beta**. or a deriv. or analog of **TGF.beta**.. The exposure is advantageously in conjunction with one or more antigens of a prospective father so that a hyporesponsive immune reaction is mounted to the one or more antigens of the prospective father. The treatment illicts a transient hyporesponsive immune reaction that alleviates symptoms of the infertility condition. Methods are also claimed for diagnosing an infertility condition in males by testing the level of **TGF**. **beta**. in the seminal fluid and in females by testing for the capacity of the female to convert the inactive form of **TGF**. **beta**. to the active form. Some specific disorders or procedures that may benefit from the present invention are: recurrent miscarriage, IVF treatment, anti-sperm antibody therapy, pre-eclampsia and intra-uterine growth restriction, prospective anal. of stud animal fertility in livestock breeding industries, and optimization of pregnancy outcome in livestock breeding industries.

ST infertility treatment diagnosis TGFbeta activin; paternal antigen TGFbeta infertility treatment diagnosis

IT Platelet (blood)
(**TGF.beta**. administration in the form of platelets; treatment and diagnosis of infertility using **TGF** **.beta**. or activin in conjunction with one or more antigens of a prospective father)

IT Antibodies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anti-sperm antibody therapy; treatment and diagnosis of infertility using **TGF.beta**. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Semen
Seminal plasma
(antigen administration in; treatment and diagnosis of infertility using **TGF.beta**. or activin in conjunction with one or more antigens of a prospective father)

IT Leukocyte
Sperm
(**antigen** administration on; treatment and diagnosis of infertility using **TGF.beta**. or activin in conjunction with one or more antigens of a prospective father)

IT Livestock
(breeding; treatment and diagnosis of infertility using **TGF** **.beta**. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs. or analogs; treatment and diagnosis of infertility using **TGF.beta**. or activin in conjunction with one or more

antigens of a prospective father)
IT Uterine diseases
(intra-uterine growth restriction; treatment and diagnosis of infertility using **TGF.beta.** or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)
IT Breeding (animal)
(livestock; treatment and diagnosis of infertility using **TGF.beta.** or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)
IT Diagnosis
Infertility (animal)
(treatment and diagnosis of infertility using **TGF.beta.** or activin in conjunction with one or more antigens of a prospective father)
IT Antigens
Class I MHC antigens
MHC antigens
Transforming growth factor .beta.1
Transforming growth factor .beta.**2**
Transforming growth factor .beta.3
Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment and diagnosis of infertility using **TGF.beta.** or activin in conjunction with one or more antigens of a prospective father)
IT Abortion (spontaneous)
In vitro fertilization (animal)
Preeclampsia
(treatment and diagnosis of infertility using **TGF.beta.** or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)
IT Drug delivery systems
Vaginal drug delivery systems
(treatment and diagnosis of infertility using compns. contg. **TGF.beta.** or activin in conjunction with one or more antigens of a prospective father)

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=> s l2 and immune tolerance

L4 165 L2 AND IMMUNE TOLERANCE

=> s l4 and implantation

L5 1 L4 AND IMPLANTATION

=> d l5 all

L5 ANSWER 1 OF 1 MEDLINE
AN 93252646 MEDLINE
DN 93252646
TI Transforming growth factor-beta (**TGF-beta**)-mediated immunosuppression in the tumor-bearing state: enhanced production of **TGF-beta** and a progressive increase in **TGF-beta** susceptibility of anti-tumor CD4+ T cell function.
AU Li X F; Takiuchi H; Zou J P; Katagiri T; Yamamoto N; Nagata T; Ono S; Fujiwara H; Hamaoka T
CS Biomedical Research Center, Osaka University Medical School.
SO JAPANESE JOURNAL OF CANCER RESEARCH, (1993 Mar) 84 (3) 315-25. Journal code: HBA. ISSN: 0910-5050.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199308
AB The present study deals with the effect of transforming growth factor-beta (**TGF-beta**) on anti-tumor immune responsiveness at various stages of the tumor-bearing state. Spleen cells from BALB/c mice bearing a syngeneic tumor (CSA1M) 1-3 wk after inoculation with CSA1M cells produced interleukin-**2** (IL-**2**) and macrophage-activating factor (MAF)/interferon-gamma (IFN-gamma) upon in vitro culture without addition of exogenous tumor antigens. This lymphokine production was achieved through collaboration between anti-CSA1M CD4+ T cells and antigen-presenting cells that had been pulsed with CSA1M tumor antigens in vivo in the tumor-bearing state. The IL-**2**-producing capacity of CD4+ T cells reached the maximal level as early as one week after tumor **implantation** but decreased with the progress of tumor-bearing stages. In contrast, the capacity of CD4+ T cells to produce MAF/IFN-gamma was not affected but was maintained at high levels even late in the tumor-bearing state. The addition of recombinant **TGF-beta** (rTGF-beta) to cultures of spleen cells from various tumor-bearing stages resulted in the suppression of lymphokine production. However, the magnitude of the **TGF-beta**-induced suppression varied depending on which tumor-bearing stages of splenic cells were tested as a responding cell population; it was slight in cells from early (1-3 wk) tumor-bearing stages but increased in cells from donor mice at later tumor-bearing stages. Thus, spleen cells from late tumor-bearing stages with weak but significant IL-**2**-producing and considerable MAF/IFN-gamma producing capacities failed to produce these lymphokines when rTGF-beta was present in cultures. A progressive increase in the **TGF-beta** susceptibility was also observed for IL-4-producing Th2 as well as IL-**2**/MAF-producing Th1 cells. In addition, increased levels of **TGF-beta** were detected in plasma from tumor-bearing mice at late stages. Taken together, these results indicate that tumor-bearing mice exhibit enhanced production of **TGF-beta** as well as a progressive increase in the susceptibility of anti-tumor CD4+ T cells to **TGF-beta**-induced suppressive mechanisms.
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Cell Division: IM, immunology

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*CD4-Positive T-Lymphocytes: IM, immunology
Dose-Response Relationship, Drug
*Fibrosarcoma: IM, immunology
***Immune Tolerance: DE, drug effects**
Interferon Type II: BI, biosynthesis
Interleukin-2: BI, biosynthesis
Interleukin-4: BI, biosynthesis
Macrophage-Activating Factors: BI, biosynthesis
Mice
Mice, Inbred BALB C
Spleen: IM, immunology
T-Lymphocytes, Cytotoxic: PH, physiology
T-Lymphocytes, Helper-Inducer: IM, immunology
Time Factors
Transforming Growth Factor beta: BI, biosynthesis
*Transforming Growth Factor beta: PD, pharmacology
Tumor Cells, Cultured
RN 82115-62-6 (Interferon Type II)
CN 0 (Interleukin-**2**); 0 (Interleukin-4); 0 (Macrophage-Activating Factors); 0 (Transforming Growth Factor beta)

=> s Transforming growth factor beta-2

L6 3106 TRANSFORMING GROWTH FACTOR BETA-2

=> s l6 and maternal immune tolerance

L7 0 L6 AND MATERNAL IMMUNE TOLERANCE

=> s l6 and fertility

L8 2 L6 AND FERTILITY

=> d l8 all 1-2

L8 ANSWER 1 OF 2 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1998:920054 SCISEARCH
GA The Genuine Article (R) Number: 142QY
TI The bone morphogenetic protein 15 gene is X-linked and expressed in oocytes
AU Dube J L; Wang P; Elvin J; Lyons K M; Celeste A J; Matzuk M M (Reprint)
CS BAYLOR COLL MED, DEPT PATHOL, 1 BAYLOR PLAZA, HOUSTON, TX 77030 (Reprint);
BAYLOR COLL MED, DEPT PATHOL, HOUSTON, TX 77030; BAYLOR COLL MED, DEPT CELL BIOL, HOUSTON, TX 77030; BAYLOR COLL MED, DEPT HUMAN MOL GENET, HOUSTON, TX 77030; GENET INST INC, DEPT TISSUE GROWTH & REPAIR, CAMBRIDGE,
MA 02140; UNIV CALIF LOS ANGELES, SCH MED, DEPT ORTHOPAED SURG, LOS ANGELES, CA 90095; UNIV CALIF LOS ANGELES, SCH MED, DEPT BIOL CHEM, LOS ANGELES, CA 90095
CYA USA
SO MOLECULAR ENDOCRINOLOGY, (DEC 1998) Vol. 12, No. 12, pp. 1809-1817.
Publisher: ENDOCRINE SOC, 4350 EAST WEST HIGHWAY SUITE 500, BETHESDA, MD 20814-4110.
ISSN: 0888-8809.

DT Article; Journal
FS LIFE
LA English
REC Reference Count: 35
AB We have taken advantage of the sequence relationships among the bone morphogenetic proteins (BMPs) to identify the mouse Bmp15 and human BMP15 genes. The 392-amino acid prepropeptides encoded by these BMP genes exhibit significant homology to each other, although the 70% identity observed between the 125-amino acid mature peptides is considerably lower than that seen in comparisons of other mouse and human orthologs. Both genes share a common structural organization and encode mature peptides that lack the cysteine residue normally involved in the formation of a covalent dimer. In addition, mouse Bmp15 and human BMP15 map to conserved syntenic regions on the X chromosome. We demonstrate, through a combination of Northern blot and in situ hybridization analyses, that mouse Bmp15 is expressed specifically in the oocyte beginning at the one-layer primary follicle stage and continuing through ovulation. Interestingly, BMP-15 is most closely related to and shares a coincident expression pattern with the mouse growth/differentiation factor 9 (GDF-9) gene that is essential for female **fertility**. Our findings will be important for defining the role of BMP-15 in follicular development.
CC ENDOCRINOLOGY & METABOLISM
STP KeyWords Plus (R): GROWTH-FACTOR-BETA; HUMAN OSTEOGENIC PROTEIN-1; **TRANSFORMING GROWTH-FACTOR-BETA-2**; CRYSTAL-STRUCTURE; IN-VIVO; SUPERFAMILY; MEMBERS; FAMILY; MOUSE; HYBRIDIZATION
RE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
ALBRECHT U	1997		23	MOL CELLULAR METHODS
AONO A	1995	210	670	BIOCHEM BIOPH RES CO
BALDINI A	1992	14	181	GENOMICS
BEHRINGER R R	1994	79	415	CELL
BOYD Y	1997	7	313	MAMM GENOME
CELESTE A J	1990	87	9843	P NATL ACAD SCI USA
CHEIFETZ S	1988	263	10783	J BIOL CHEM
DAOPIN S	1992	257	369	SCIENCE
DONG L W	1996	9	383	J MOL RECOGNIT
DUDLEY A T	1995	9	2795	GENE DEV
GRIFFITH D L	1996	93	878	P NATL ACAD SCI USA
HOGAN B L M	1996	10	1580	GENE DEV
ISRAEL D I	1996	13	291	GROWTH FACTORS
JONES C M	1992	6	1961	MOL ENDOCRINOL
KINGSLEY D M	1992	71	399	CELL
KINGSLEY D M	1994	8	133	GENE DEV
KUSUMOTO K	1997	239	575	BIOCHEM BIOPH RES CO
LAU A L	1997		220	INHIBIN ACTIVIN FOLL
MAHMOUDI M	1989	7	331	BIOTECHNIQUES
MATHER J P	1997	215	209	P SOC EXP BIOL MED
MCGRATH S A	1995	9	131	MOL ENDOCRINOL
MCPHERRON A C	1993	268	3444	J BIOL CHEM
OZKAYNAK E	1992	267	25220	J BIOL CHEM
PEDERSEN T	1968	17	555	J REPROD FERTIL
ROSEN V	1996		661	PRINCIPLES BONE BIOL
ROWE L B	1994	5	253	MAMM GENOME
SAMPATH T K	1992	267	20352	J BIOL CHEM
SCHLUNEGGER M P	1993	231	445	J MOL BIOL

TATUSOV R L	1997	278	631	SCIENCE
WANG E A	1990	87	2220	P NATL ACAD SCI USA
WINNIER G	1995	9	2105	GENE DEV
WOLFMAN N M	1997	100	321	J CLIN INVEST
ZHANG H B	1996	122	2977	DEVELOPMENT
ZHAO G Q	1998	125	1103	DEVELOPMENT
ZHAO G Q	1996	10	1657	GENE DEV

L8 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AN 1998:618828 CAPLUS
DN 129:212101
TI Treatment and diagnosis of infertility using TGF.beta. or activin
IN Robertson, Sarah Anne; Tremellen, Kelton Paul
PA Luminis Pty. Ltd., Australia
SO PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-18
ICS A61K039-00; G01N033-68
CC 2-3 (Mammalian Hormones)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9839021	A1	19980911	WO 1998-AU149	19980306
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9862846	A1	19980922	AU 1998-62846	19980306
	AU 722150	B2	20000720		
	EP 1028743	A1	20000823	EP 1998-906749	19980306
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI AU 1997-5508 19970306
WO 1998-AU149 19980306

AB A method of treating an infertility condition in humans or mammals, by exposure of a prospective mother to TGF.beta. or a deriv. or analog of TGF.beta.. The exposure is advantageously in conjunction with one or more antigens of a prospective father so that a hyporesponsive immune reaction is mounted to the one or more antigens of the prospective father. The treatment illicts a transient hyporesponsive immune reaction that alleviates symptoms of the infertility condition. Methods are also claimed for diagnosing an infertility condition in males by testing the level of TGF.beta. in the seminal fluid and in females by testing for the capacity of the female to convert the inactive form of TGF.beta. to the active form. Some specific disorders or procedures that may benefit from the present invention are: recurrent miscarriage, IVF treatment, anti-sperm antibody therapy, pre-eclampsia and intra-uterine growth restriction, prospective anal. of stud animal **fertility** in livestock breeding industries, and optimization of pregnancy outcome in livestock breeding industries.

ST infertility treatment diagnosis TGFbeta activin; paternal antigen TGFbeta

infertility treatment diagnosis
IT Platelet (blood)
(TGF.beta. administration in the form of platelets; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with
one or more antigens of a prospective father)
IT Antibodies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anti-sperm antibody therapy; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)
IT Semen
Seminal plasma
(antigen administration in; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)
IT Leukocyte
Sperm
(antigen administration on; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)
IT Livestock
(breeding; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)
IT Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs. or analogs; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)
IT Uterine diseases
(intra-uterine growth restriction; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)
IT Breeding (animal)
(livestock; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)
IT Diagnosis
Infertility (animal)
(treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)
IT Antigens
Class I MHC antigens
MHC antigens
Transforming growth factor .beta.1
Transforming growth factor .beta.
2
Transforming growth factor .beta.3
Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
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IT Abortion (spontaneous)
In vitro fertilization (animal)

Preeclampsia
(treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)
IT Drug delivery systems
Vaginal drug delivery systems
(treatment and diagnosis of infertility using compns. contg. TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

=> s transforming growth factor.beta.2

L9 3106 TRANSFORMING GROWTH FACTOR.BETA.2

=> s l9 and seminal plasma

L10 2 L9 AND SEMINAL PLASMA

=> d l10 all 1-2

L10 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:373527 BIOSIS
DN PREV199900373527
TI A sensitive and specific in vitro bioassay for activin using a mouse plasmacytoma cell line, MPC-11.
AU Phillips, D. J. (1); Brauman, J. N.; Mason, A. J.; de Kretser, D. M.; Hedger, M. P.
CS (1) Monash Medical Centre, Institute of Reproduction and Development, 246 Clayton Road, Level 3, Block E, Clayton, VIC, 3168 Australia
SO Journal of Endocrinology, (July, 1999) Vol. 162, No. 1, pp. 111-116. ISSN: 0022-0795.
DT Article
LA English
SL English
AB A new in vitro bioassay for activin was developed using the mouse plasmacytoma cell line, MPC-11. Human recombinant (hr) activin A dose-dependently inhibited the proliferation of these cells, whereas a range of other factors, including inhibin, follistatin and transforming growth factor-beta1, -beta2 and -beta3 had no effect. Conditioned medium containing activin B induced an inhibition similar to hr-activin A. The inhibitory influence of activin A could be blocked by follistatin, but not by hr-inhibin A. This bioassay had a sensitivity for activin A of around 0.4 ng/ml, an ED50 response of 3.5 ng/ml, and an intraassay coefficient of variation of <11%. It offers substantial advantages over existing in vitro activin bioassays in terms of ease of use, specificity and throughput. The utility of the MPC-11 bioassay was demonstrated in the purification of activin from amniotic fluid, where an almost identical profile of bioactive activin A was detected compared with the pituitary cell bioassayof activin. Bioactive activin could also be detected in unpurified ovine allantoic and amniotic fluids and bovine follicular fluid. Measuring

activin in untreated and heat-treated human sera or **seminal plasma** was hampered by a non-specific inhibitory effect, so that several serum samples did not run parallel with the hr-activin A standard.

This inhibitory effect by serum could not be overcome by addition of follistatin, suggesting it is not activin-like bioactivity. This new bioassay for activin demonstrates widespread applicability for monitoring of purified or partially purified samples during purification procedures, bioactivity measurements, receptor-binding studies and assays of cell culture medium.

CC Endocrine System - General *17002
Developmental Biology - Embryology - General and Descriptive *25502
BC Muridae 86375
IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Methods and Techniques
IT Parts, Structures, & Systems of Organisms
amniotic fluid: embryonic structure
IT Chemicals & Biochemicals
activin; follistatin; inhibin; recombinant activin; transforming growth factor-beta 1; **transforming growth factor -beta 2**; transforming growth factor-beta 3
IT Methods & Equipment
in vitro bioassay: analytical method
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
MPC-11 cell line (Muridae): plasmacytoma cell
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 57285-09-3 (INHIBIN)
117628-82-7 (FOLLISTATIN)

L10 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AN 1998:618828 CAPLUS
DN 129:212101
TI Treatment and diagnosis of infertility using TGF.beta. or activin
IN Robertson, Sarah Anne; Tremellen, Kelton Paul
PA Luminis Pty. Ltd., Australia
SO PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-18
ICS A61K039-00; G01N033-68
CC 2-3 (Mammalian Hormones)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9839021	A1	19980911	WO 1998-AU149	19980306

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,

FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9862846 A1 19980922 AU 1998-62846 19980306
AU 722150 B2 20000720
EP 1028743 A1 20000823 EP 1998-906749 19980306
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRAI AU 1997-5508 19970306
WO 1998-AU149 19980306

AB A method of treating an infertility condition in humans or mammals, by exposure of a prospective mother to TGF.beta. or a deriv. or analog of TGF.beta.. The exposure is advantageously in conjunction with one or more antigens of a prospective father so that a hyporesponsive immune reaction is mounted to the one or more antigens of the prospective father. The treatment illicts a transient hyporesponsive immune reaction that alleviates symptoms of the infertility condition. Methods are also claimed for diagnosing an infertility condition in males by testing the level of TGF.beta. in the seminal fluid and in females by testing for the capacity of the female to convert the inactive form of TGF.beta. to the active form. Some specific disorders or procedures that may benefit from the present invention are: recurrent miscarriage, IVF treatment, anti-sperm antibody therapy, pre-eclampsia and intra-uterine growth restriction, prospective anal. of stud animal fertility in livestock breeding industries, and optimization of pregnancy outcome in livestock breeding industries.

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IT Leukocyte
Sperm
(antigen administration on; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

IT Livestock
(breeding; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs. or analogs; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

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(treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)
IT Antigens
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MHC antigens
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Transforming growth factor .beta.
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Transforming growth factor .beta.3
Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
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IT Abortion (spontaneous)
In vitro fertilization (animal)
Preeclampsia
(treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)
IT Drug delivery systems
Vaginal drug delivery systems
(treatment and diagnosis of infertility using compns. contg. TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

=> d his

(FILE 'HOME' ENTERED AT 11:16:33 ON 19 FEB 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:16:57 ON 19 FEB 2001

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L1         68514 S TGF BETA
L2         27819 S L1 AND 2
L3             1 S L2 AND SPERM ANTIGEN
L4           165 S L2 AND IMMUNE TOLERANCE
L5             1 S L4 AND IMPLANTATION
L6          3106 S TRANSFORMING GROWTH FACTOR BETA-2
L7             0 S L6 AND MATERNAL IMMUNE TOLERANCE
L8             2 S L6 AND FERTILITY
L9          3106 S TRANSFORMING GROWTH FACTOR.BETA.2
L10            2 S L9 AND SEMINAL PLASMA
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=> s l9 and trophoblast

L11 37 L9 AND TROPHOBLAST

=> s l11 and fibronectin

L12 3 L11 AND FIBRONECTIN

=> d l12

L12 ANSWER 1 OF 3 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:192912 BIOSIS
DN PREV199799492115
TI Expression of TGF-beta and extracellular matrix proteins at the fetomaternal interface of developing placentas in first trimester.
AU Nemoto, N. (1); Hayakawa, S.; Chishima, F.; Kinukawa, N.; Sakurai, I.; Segi, K.; Satoh, K.
CS (1) Dep. Pathol., Nihon Univ. Sch. Med., Tokyo 173 Japan
SO Pathology International, (1996) Vol. 46, No. SUPPL. 1, pp. 681.
Meeting Info.: XXI International Congress of the International Academy of Pathology and 12th World Congress of Academic and Environmental Pathology Budapest, Hungary October 20-25, 1996
ISSN: 1320-5463.
DT Conference; Abstract; Conference
LA English

=> d l12 all 1-3

L12 ANSWER 1 OF 3 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:192912 BIOSIS
DN PREV199799492115
TI Expression of TGF-beta and extracellular matrix proteins at the fetomaternal interface of developing placentas in first trimester.
AU Nemoto, N. (1); Hayakawa, S.; Chishima, F.; Kinukawa, N.; Sakurai, I.; Segi, K.; Satoh, K.
CS (1) Dep. Pathol., Nihon Univ. Sch. Med., Tokyo 173 Japan
SO Pathology International, (1996) Vol. 46, No. SUPPL. 1, pp. 681.
Meeting Info.: XXI International Congress of the International Academy of Pathology and 12th World Congress of Academic and Environmental Pathology Budapest, Hungary October 20-25, 1996
ISSN: 1320-5463.
DT Conference; Abstract; Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Cytology and Cytochemistry - Human *02508
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Anatomy and Histology, General and Comparative - Microscopic and Ultramicroscopic Anatomy *11108
Metabolism - Proteins, Peptides and Amino Acids *13012
Reproductive System - Anatomy *16502
Reproductive System - Physiology and Biochemistry *16504
Reproductive System - Pathology *16506
Endocrine System - General *17002
Developmental Biology - Embryology - General and Descriptive *25502

Developmental Biology - Embryology - Pathological *25503
Developmental Biology - Embryology - Morphogenesis, General *25508
In Vitro Studies, Cellular and Subcellular *32600
Immunology and Immunochemistry - General; Methods *34502
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Development; Endocrine System (Chemical Coordination and Homeostasis); Immune System
(Chemical Coordination and Homeostasis); Membranes (Cell Biology); Metabolism; Morphology; Reproductive System (Reproduction)
IT Miscellaneous Descriptors
ABORTION; ADULT; ANALYTICAL METHOD; DEVELOPMENT; EMBRYO; EMBRYONIC STRUCTURE; ENDOCRINE SYSTEM; EXPRESSION; EXTRACELLULAR MATRIX PROTEINS;
FEMALE; FETOMATERNAL INTERFACE; FETUS; **FIBRONECTIN**; FIRST TRIMESTER; IMMUNOHISTOCHEMISTRY; IMMUNOLOGIC METHOD; IN-VITRO; PATIENT;
PLACENTA; PREGNANCY RELATED DISEASE; REPRODUCTIVE SYSTEM; REPRODUCTIVE SYSTEM DISEASE/FEMALE; TENASCIN; TGF-BETA-1; TGF-BETA-2; TRANSFORMING GROWTH FACTOR-BETA-1; **TRANSFORMING GROWTH FACTOR-BETA-2**; **TROPHOBLAST**;
TROPHOBLASTIC GROWTH; TROPHOBLASTIC INVASION; TROPHOBLASTIC MIGRATION
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L12 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2001 ACS
AN 1998:621378 CAPLUS
DN 129:257363
TI Regulation of **trophoblast** invasion and diagnosis of preeclampsia
IN Caniggia, Isabella; Post, Martin; Lye, Stephen
PA Mount Sinai Hospital Corp., Can.; Hospital for Sick Children
SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM G01N033-68
ICS G01N033-566; C07K014-47
CC 9-16 (Biochemical Methods)
Section cross-reference(s): 2, 3, 6, 13, 14
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9840747	A1	19980917	WO 1998-CA180	19980305
	W: AU, CA, JP, MX, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9862871	A1	19980929	AU 1998-62871	19980305
	EP 968430	A1	20000105	EP 1998-906777	19980305
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	US 1997-39919		19970307		
	WO 1998-CA180		19980305		

AB Methods are provided for the diagnosis and treatment of patients with

increased risk of preeclampsia. The invention describes mechanisms that regulate **trophoblast** invasion. The inventors have found that antisense disruption of the expression of the TGF.beta. receptor, endoglin, triggers invasion of cytotrophoblast from first trimester villous explants in vitro indicating that the TGF.beta. receptor system, and in particular endoglin, plays a crit. role in regulating this process.

Broadly stated the present invention relates to a method for detecting, preventing, and/or treating a condition requiring regulation of **trophoblast** invasion by modulating (a) TGF.beta.3, (b) receptors of cytokines of the TGF.beta. family, (c) HIF-1.alpha., and/or (d) O2 tension. A method is also described for diagnosing increased risk of preeclampsia in a subject comprising detecting TGF.beta.3 or its receptors, or HIF-1.alpha. in a sample from the subject.

ST **trophoblast** invasion pregnancy preeclampsia diagnosis

IT Transcription factors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(HIF-1 (hypoxia-inducible factor 1), alpha; regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Carcinoma inhibitors
(choriocarcinoma; regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Choriocarcinoma
(inhibitors; regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Blood analysis
Choriocarcinoma
Diagnosis
Drug screening
Placenta
Preeclampsia
Pregnancy
Pregnancy disorders
Trophoblast
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Transforming growth factor .beta.3
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Cytokine receptors
Transforming growth factor .beta. receptors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Antisense DNA
Antisense oligonucleotides
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT **Fibronectins**
Integrin .alpha.5
Transforming growth factor .beta.1
Transforming growth factor .beta.
2
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Endoglins
Transforming growth factor .beta. type I receptors
Transforming growth factor .beta. type II receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Decorins
Fetuins
Thyroglobulin
.alpha.2-Macroglobulins
RL: BPR (Biological process); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Antibodies
RL: BPR (Biological process); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(to TGF.beta.3; regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT 146480-36-6, Gelatinase B 213322-42-0 213322-45-3 213322-46-4
213322-47-5 213322-48-6 213394-93-5
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT 7782-44-7, Oxygen, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

L12 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2001 ACS
AN 1997:675833 CAPLUS
DN 127:355610
TI Endoglin regulates **trophoblast** differentiation along the invasive pathway in human placental villous explants
AU Caniggia, Isabella; Taylor, Carolyn V.; Knox Ritchie, J. W.; Lye, Stephen J.; Letarte, Michelle
CS Program Fetal Health and Development, Sanuel Lunenfeld Res. Inst., Univ. Toronto, Toronto, ON, M5G 1X5, Can.
SO Endocrinology (1997), 138(11), 4977-4988
CODEN: ENDOAO; ISSN: 0013-7227
PB Endocrine Society
DT Journal
LA English
CC 2-10 (Mammalian Hormones)

AB Successful invasion of the maternal vascular system by **trophoblast** cells in a prerequisite for the establishment of a normal hemochorial placenta. Transforming growth factor-.beta. (THF.beta.) has been implicated in the regulation of **trophoblast** invasiveness into the uterus. Endoglin is a component of the TGF.beta. receptor complex that binds .beta.1 and .beta.3 isoforms and is expressed at high levels on syncytiotrophoblast throughout pregnancy and is also transiently up-regulated on extra-villous **trophoblasts** differentiating along the invasive pathway. The authors investigated the role of endoglin in a serum-free human villous explant culture system that allows the study of **trophoblast** outgrowth, migration, and invasion and mimics events occurring in anchoring villi during the first trimester of gestation. Addn. to explant cultures from 5-8 wk gestation of a monoclonal antibody to endoglin or of antisense endoglin oligonucleotides significantly stimulated **trophoblast** outgrowth and migration. These responses were specific, as incubation of explants with nonimmune IgG or sense and scrambled oligonucleotides had no effect. Antisense endoglin-induced **trophoblast** outgrowth and migration were accompanied by cell division of villous-assocd. **trophoblasts** within the proximal region of the forming column and by the characteristic switch in integrins obsd. in anchoring villi in situ. Treatment of villous explants with antibody and antisense oligonucleotides to endoglin also resulted in an increased **fibronectin** release into the culture medium. The stimulatory effect of antisense endoglin on **fibronectin** prodn. was overcome by the addn. of exogenous TGF.beta.2, but not TGF.beta.1 and -.beta.3. These findings suggest that endoglin expression in the transition from polarized to nonpolarized **trophoblasts** in anchoring villi is necessary for mediation of the inhibitory effect of TGF.beta.1 and/or TGF.beta.3 on **trophoblast** differentiation along the invasive pathway.

ST endoglin **trophoblast** differentiation invasive pathway; TGF **trophoblast** differentiation placenta endoglin

IT Cell differentiation
Cell division
Cell migration
Trophoblast
Uterus
(endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

IT Transforming growth factor .beta.1
Transforming growth factor .beta. 2
Transforming growth factor .beta.3
Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

IT Integrin .alpha.5
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

IT Keratins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

IT Transforming growth factor .beta. receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)
IT **Fibronectins**
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)
IT Glycoproteins (specific proteins and subclasses)
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(endoglins; endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)
IT Pregnancy
(first trimester; endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)
IT Placenta
(villus; endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)
IT Integrins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(.alpha.6; endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

=> d his

(FILE 'HOME' ENTERED AT 11:16:33 ON 19 FEB 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:16:57 ON 19 FEB 2001

L1 68514 S TGF BETA
L2 27819 S L1 AND 2
L3 1 S L2 AND SPERM ANTIGEN
L4 165 S L2 AND IMMUNE TOLERANCE
L5 1 S L4 AND IMPLANTATION
L6 3106 S TRANSFORMING GROWTH FACTOR BETA-2
L7 0 S L6 AND MATERNAL IMMUNE TOLERANCE
L8 2 S L6 AND FERTILITY
L9 3106 S TRANSFORMING GROWTH FACTOR.BETA.2
L10 2 S L9 AND SEMINAL PLASMA
L11 37 S L9 AND TROPHOBLAST
L12 3 S L11 AND FIBRONECTIN

=> s l11 and tropho ulteronectin

L13 0 L11 AND TROPHO ULTERONECTIN

=> s l11 and uteronectin

L14 0 L11 AND UTERONECTIN

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=> s l11 and tropho-uteronectin

L15           0 L11 AND TROPHO-UTERONECTIN

=> d his


     (FILE 'HOME' ENTERED AT 11:16:33 ON 19 FEB 2001)

     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:16:57 ON
     19 FEB 2001
L1         68514 S TGF BETA
L2         27819 S L1 AND 2
L3             1 S L2 AND SPERM ANTIGEN
L4           165 S L2 AND IMMUNE TOLERANCE
L5             1 S L4 AND IMPLANTATION
L6          3106 S TRANSFORMING GROWTH FACTOR BETA-2
L7             0 S L6 AND MATERNAL IMMUNE TOLERANCE
L8             2 S L6 AND FERTILITY
L9          3106 S TRANSFORMING GROWTH FACTOR.BETA.2
L10            2 S L9 AND SEMINAL PLASMA
L11           37 S L9 AND TROPHOBLAST
L12            3 S L11 AND FIBRONECTIN
L13            0 S L11 AND TROPHO ULTERONECTIN
L14            0 S L11 AND UTERONECTIN
L15            0 S L11 AND TROPHO-UTERONECTIN

=> s l9 and immunomodulation

L16           16 L9 AND IMMUNOMODULATION

=> dup remove l16

PROCESSING COMPLETED FOR L16
L17           16 DUP REMOVE L16 (0 DUPLICATES REMOVED)

=> d l17 1-16


L17  ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2001 ACS
AN   2000:82564  CAPLUS
DN   132:221258
TI   Analysis of immunomodulatory activities of aqueous humor from eyes of
mice
     with experimental autoimmune uveitis
AU   Ohta, Kouichi; Wiggert, Barbara; Yamagami, Satoru; Taylor, Andrew W.;
     Streilein, J. Wayne
CS   Schepens Eye Research Institute and Department of Ophthalmology, Harvard
     Medical School, Boston, MA, 02114, USA
SO   J. Immunol. (2000), 164(3), 1185-1192
     CODEN: JOIMA3; ISSN: 0022-1767
PB   American Association of Immunologists
DT   Journal
LA   English
RE.CNT  48
RE
(1) Agarwal, R; J Immunol 1999, V162, P2648 CAPLUS
```

(2) Apte, R; J Immunol 1998, V160, P5693 CAPLUS
(12) Gijbels, K; Mol Med 1995, V1, P795 CAPLUS
(14) Granstein, R; J Immunol 1990, V144, P3021 CAPLUS
(15) Hara, Y; J Immunol 1992, V148, P1685 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000429287 EMBASE
TI **Transforming growth factor .beta.**
2 (TGF.beta.2) produces effective pleurodesis in sheep with no systemic complications.
AU Lee Y.C.G.; Lane K.B.; Parker R.E.; Ayo D.S.; Rogers J.T.; Diters R.W.; Thompson P.J.; Light R.W.
CS Dr. Y.C.G. Lee, Department of Pulmonary Medicine, St Thomas Hospital, 4220
Harding Road, Nashville, TN 37202, United States. ycgarylee@hotmail.com
SO Thorax, (2000) 55/12 (1058-1062).
Refs: 32
ISSN: 0040-6376 CODEN: THORA7
CY United Kingdom
DT Journal; Article
FS 015 Chest Diseases, Thoracic Surgery and Tuberculosis
037 Drug Literature Index
LA English
SL English

L17 ANSWER 3 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000406101 EMBASE
TI Nitric oxide augments release of chemokines from monocytic U937 cells: Modulation by anti-inflammatory pathways.
AU Muhl H.; Chang J.-H.; Huwiler A.; Bosmann M.; Paulukat J.; Ninic R.; Nold M.; Hellmuth M.; Pfeilschifter J.
CS Dr. H. Muhl, Pharmazentrum Frankfurt, Klinikum der Johann Wolfgang Goethe,
Universitat Frankfurt am Main, Theodor-Stern-Kai 7, D-65090 Frankfurt am Main, Germany. H.Muehl@em.uni-frankfurt.de
SO Free Radical Biology and Medicine, (15 Nov 2000) 29/10 (969-980).
Refs: 73
ISSN: 0891-5849 CODEN: FRBMEH
PUI S 0891-5849(00)00389-0
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English

L17 ANSWER 4 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000076625 EMBASE
TI Human astrocytomas co-expressing Fas and Fas ligand also produce TGF.beta.2 and Bcl-2.
AU Frankel B.; Longo S.L.; Ryken T.C.
CS B. Frankel, Department of Neurosurgery, SUNY Health Science Ctr. at Syracuse, 750 East Adams St., Syracuse, NY 13210, United States. frankelb@vax.cs.hscsyr.edu
SO Journal of Neuro-Oncology, (1999) 44/3 (205-212).
Refs: 42

ISSN: 0167-594X CODEN: JNODD2
CY United States
DT Journal; Article
FS 016 Cancer
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LA English
SL English

L17 ANSWER 5 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998184687 EMBASE
TI Differential effects of IGF-1 and TGF.beta.-2 on the assembly of proteoglycans in pericellular and territorial matrix by cultured bovine articular chondrocytes.
AU Van Osch G.J.V.M.; Van den Berg W.B.; Hunziker E.B.; Hauselmann H.J.
CS G.J.V.M. Van Osch, Department of Otorhinolaryngology, University of Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, Netherlands
SO Osteoarthritis and Cartilage, (1998) 6/3 (187-195).
Refs: 35
ISSN: 1063-4584 CODEN: OSCAEO
CY United Kingdom
DT Journal; Article
FS 031 Arthritis and Rheumatism
037 Drug Literature Index
LA English
SL English

L17 ANSWER 6 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998289098 EMBASE
TI The effect of cytokine mediators on prostaglandin inhibition by human decidual cells.
AU Young Ju Kim; Jung Ja Ahn; Bock Hi Woo
CS Dr. Y.J. Kim, Dept. of Obstetrics and Gynecology, Ewha Womans University Hospital, 911-1 MokDong, Yangcheonku, Seoul 158-056, Korea, Republic of
SO American Journal of Obstetrics and Gynecology, (1998) 179/1 (146-149).
Refs: 18
ISSN: 0002-9378 CODEN: AJOGAH
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
010 Obstetrics and Gynecology
LA English
SL English

L17 ANSWER 7 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97253297 EMBASE
DN 1997253297
TI Antisense oligonucleotides specific for **transforming growth factor .beta.2** inhibit the growth of malignant mesothelioma both in vitro and in vivo.
AU Marzo A.L.; Fitzpatrick D.R.; Robinson B.W.S.; Scott B.
CS A.L. Marzo, Western Australia Univ. Dept. Med., Queen Elizabeth II Medical Centre, Verdum Street, Nedlands, WA 6008, Australia.
amarzo@uniwa.uwa.edu.au
SO Cancer Research, (1997) 57/15 (3200-3207).
Refs: 35

ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
021 Developmental Biology and Teratology
LA English
SL English

L17 ANSWER 8 OF 16 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1998:77371 SCISEARCH
GA The Genuine Article (R) Number: YQ954
TI Spectrum of immunomodulating agents in human milk
AU Goldman A S (Reprint); Chheda S; Garofalo R
CS UNIV TEXAS, MED BRANCH, DEPT PEDIAT, 301 UNIV BLVD, GALVESTON, TX 77555 (Reprint)
CYA USA
SO INTERNATIONAL JOURNAL OF PEDIATRIC HEMATOLOGY/ONCOLOGY, (MAR 1997) Vol. 4,
No. 5, pp. 491-497.
Publisher: HARWOOD ACAD PUBL GMBH, C/O STBS LTD, PO BOX 90, READING, BERKS, ENGLAND RG1 8JL.
ISSN: 1070-2903.
DT Article; Journal
FS CLIN
LA English
REC Reference Count: 71
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L17 ANSWER 9 OF 16 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:310009 BIOSIS
DN PREV199699032365
TI Alpha-fetoprotein (AFP) mediated immunoregulation is not associated with **transforming growth factor-beta** **2** (TGF-beta-2.
AU Semeniuk, D. J.; Murgita, R. A.
CS Dep. Microbiol. Immunol., McGill Univ., Montreal, PQ H3A 2B4 Canada
SO FASEB Journal, (1996) Vol. 10, No. 6, pp. A1442.
Meeting Info.: Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for Investigative Pathology and the American Association of Immunologists New Orleans, Louisiana, USA June
2-6, 1996
ISSN: 0892-6638.
DT Conference
LA English

L17 ANSWER 10 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97017166 EMBASE
DN 1997017166
TI **Transforming growth factor-.beta.**
2-mediated regulation of C3 gene expression in monocytes.
AU Drouin S.M.; Carlino J.A.; Barnum S.R.
CS S.R. Barnum, Department of Microbiology, University of Alabama at Birmingham, 1918 University Boulevard, Birmingham, AL 35294, United States
SO Molecular Immunology, (1996) 33/13 (1025-1034).
Refs: 45
ISSN: 0161-5890 CODEN: IMCHAZ

PUI S 0161-5890(96)00071-5
CY United Kingdom
DT Journal; Article
FS 025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English

L17 ANSWER 11 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96136702 EMBASE
DN 1996136702
TI **Transforming growth factor-.beta.**
2-related-decidual suppressor factor is not related to TJ6 protein.
AU Merali F.S.; Arck P.C.; Beaman K.; Clark D.A.
CS Department of Medicine, McMaster University,Hamilton, Ont., Canada
SO American Journal of Reproductive Immunology, (1996) 35/4 (342-347).
ISSN: 8755-8920 CODEN: AAJID6
CY Denmark
DT Journal; Conference Article
FS 010 Obstetrics and Gynecology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LA English
SL English

L17 ANSWER 12 OF 16 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:111128 BIOSIS
DN PREV199799410331
TI Immunomodulatory activity of conformationally restricted peptides related to TGF-beta-2 90-99 sequence.
AU Wieczorek, Zbigniew (1); Slon, Jacek J.; Siemion, Ignacy Z.
CS (1) Inst. Immunol. Exp. Ther., Polish Acad. Sci., Czerska 12, 53-114 Wroclaw Poland
SO Archivum Immunologiae et Therapiae Experimentalis, (1996) Vol. 44, No. 4, pp. 209-214.
ISSN: 0004-069X.
DT Article
LA English

L17 ANSWER 13 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 95168099 EMBASE
DN 1995168099
TI Characterization of murine pregnancy decidua transforming growth factor .beta.. I. **Transforming growth factor .beta.2**-like molecules of unusual molecular size released in bioactive form.
AU Clark D.A.; Flanders K.C.; Hirte H.; Dasch J.R.; Coker R.; McAnulty R.J.; Laurent G.J.
CS 1200 Main Street West,Hamilton, Ont. L8N 3Z5, Canada
SO Biology of Reproduction, (1995) 52/6 (1380-1388).
ISSN: 0006-3363 CODEN: BIREBV
CY United States
DT Journal; Article
FS 010 Obstetrics and Gynecology
021 Developmental Biology and Teratology
LA English

SL English

L17 ANSWER 14 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 95269658 EMBASE
DN 1995269658
TI Systemic administration of **transforming growth factor-.beta.2** prevents the impaired bone formation and osteopenia induced by unloading in rats.
AU Machwate M.; Zerath E.; Holy X.; Hott M.; Godet D.; Lomri A.; Marie P.J.
CS INSERM Unite 349, 6 rue Guy Patin,75010 Paris, France
SO Journal of Clinical Investigation, (1995) 96/3 (1245-1253).
ISSN: 0021-9738 CODEN: JCINAO
CY United States
DT Journal; Article
FS 031 Arthritis and Rheumatism
037 Drug Literature Index
LA English
SL English

L17 ANSWER 15 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 95025765 EMBASE
DN 1995025765
TI Multiple sclerosis. Immunomodulatory effects of human astrocytes on T cells.
AU Meinl E.; Aloisi F.; Ertl B.; Weber F.; De Waal Malefyt R.; Wekerle H.; Hohlfeld R.
CS Department of Neurology, Klinikum Grosshadern, University of Munich,D-81366 Munich, Germany
SO Brain, (1994) 117/6 (1323-1332).
ISSN: 0006-8950 CODEN: BRAIAK
CY United Kingdom
DT Journal; Article
FS 008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
LA English
SL English

L17 ANSWER 16 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 92120279 EMBASE
DN 1992120279
TI Modulation of human IgE synthesis by transforming growth factor-.beta..
AU Chang You Wu; Brinkmann V.; Cox D.; Heusser C.; Delespesse G.
CS Canada
SO Clinical Immunology and Immunopathology, (1992) 62/3 (277-284).
ISSN: 0090-1229 CODEN: CLIIAT
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English

=> d his

(FILE 'HOME' ENTERED AT 11:16:33 ON 19 FEB 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:16:57 ON

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     19 FEB 2001
L1         68514 S TGF BETA
L2         27819 S L1 AND 2
L3             1 S L2 AND SPERM ANTIGEN
L4           165 S L2 AND IMMUNE TOLERANCE
L5             1 S L4 AND IMPLANTATION
L6          3106 S TRANSFORMING GROWTH FACTOR BETA-2
L7             0 S L6 AND MATERNAL IMMUNE TOLERANCE
L8             2 S L6 AND FERTILITY
L9          3106 S TRANSFORMING GROWTH FACTOR.BETA.2
L10            2 S L9 AND SEMINAL PLASMA
L11           37 S L9 AND TROPHOBLAST
L12            3 S L11 AND FIBRONECTIN
L13            0 S L11 AND TROPHO ULTERONECTIN
L14            0 S L11 AND UTERONECTIN
L15            0 S L11 AND TROPHO-UTERONECTIN
L16           16 S L9 AND IMMUNOMODULATION
L17           16 DUP REMOVE L16 (0 DUPLICATES REMOVED)

=> s 19 and knockout

L18           19 L9 AND KNOCKOUT

=> s l18 and fertility

L19            0 L18 AND FERTILITY

=> s l18 and review

L20            0 L18 AND REVIEW

=> d l18 1-19


L18  ANSWER 1 OF 19  MEDLINE
AN   97369554     MEDLINE
DN   97369554
TI   Apoptosis in adult mouse testis induced by experimental cryptorchidism.
AU   Ohta Y; Nishikawa A; Fukazawa Y; Urushitani H; Matsuzawa A; Nishina Y;
     Iguchi T
CS   Department of Veterinary Science, Faculty of Agriculture, Tottori
     University, Japan.. ohta@agr.tottori-u.ac.jp
SO   ACTA ANATOMICA, (1996) 157 (3) 195-204.
     Journal code: 09A. ISSN: 0001-5180.
CY   Switzerland
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   199710
EW   19971004

L18  ANSWER 2 OF 19  EMBASE  COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN   2000258937  EMBASE
TI   Delayed wound healing in immunodeficient TGF-.beta.1 knockout
     mice.
AU   Crowe M.J.; Doetschman T.; Greenhalgh D.G.
CS   Dr. T. Doetschman, Department of Molecular Genetics, Biochemistry and
     Microbiology, Univ. of Cincinnati Coll. of Med., 231 Bethesda Ave (ML
```

524), Cincinnati, OH 45267-0524, United States. thomas.doetschman@uc.edu
SO Journal of Investigative Dermatology, (2000) 115/1 (3-11).
Refs: 54
ISSN: 0022-202X CODEN: JIDEAE
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
013 Dermatology and Venereology
022 Human Genetics
026 Immunology, Serology and Transplantation
LA English
SL English

L18 ANSWER 3 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97245206 EMBASE
DN 1997245206
TI TGF.beta.2 **knockout** mice have multiple developmental defects that are non-overlapping with other TGF.beta. **knockout** phenotypes.
AU Sanford L.P.; Ormsby I.; Gittenberger-de Groot A.C.; Sariola H.; Friedman R.; Boivin G.P.; Cardell E.L.; Doetschman T.
CS T. Doetschman, Department of Molecular Genetics, Biochemistry and Microbiology, University of Cincinnati, Cincinnati, OH 45267, United States. thomas.doetschman@uc.edu
SO Development, (1997) 124/13 (2659-2670).
Refs: 76
ISSN: 0950-1991 CODEN: DEVPED
CY United Kingdom
DT Journal; Article
FS 001 Anatomy, Anthropology, Embryology and Histology
021 Developmental Biology and Teratology
022 Human Genetics
LA English
SL English

L18 ANSWER 4 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:487540 BIOSIS
DN PREV200000487540
TI Cardiovascular malformations in transforming growth factor-beta2 **knockout** mice relate to altered apoptosis and myocardial and endocardial cushion differentiation.
AU Bartram, U. (1); Doetschmann, T.; Speer, C. P.; Poelmann, R. E. (1); Gittenberger-de Groot, A. C. (1)
CS (1) Department of Cell Biology Neurobiology and Anatomy, University of Cincinnati, Cincinnati USA
SO European Heart Journal, (August September, 2000) Vol. 21, No. Abstract Supplement, pp. 613. print.
Meeting Info.: XXII Congress of the European Society of Cardiology Amsterdam, Netherlands August 26-30, 2000 European Society of Cardiology . ISSN: 0195-668X.
DT Conference
LA English
SL English

L18 ANSWER 5 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:63101 BIOSIS
DN PREV200000063101
TI A role for p75 neurotrophin receptor in the control of hair follicle

morphogenesis.
AU Botchkareva, Natalia V.; Botchkarev, Vladimir A.; Chen, Ling-Hong; Lindner, Gerd; Paus, Ralf (1)
CS (1) Department of Dermatology, University Hospital Eppendorf, University of Hamburg, Martinistrasse 52, D-20246, Hamburg Germany
SO Developmental Biology, (Dec. 1, 1999) Vol. 216, No. 1, pp. 135-153. ISSN: 0012-1606.
DT Article
LA English
SL English

L18 ANSWER 6 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:245507 BIOSIS
DN PREV199900245507
TI Lack of association of transforming growth factor (TGF)-beta1 and beta2 gene polymorphisms with multiple sclerosis (MS) in Northern Ireland.
AU McDonnell, G. V.; Kirk, C. W.; Hawkins, S. A.; Graham, C. A. (1)
CS (1) Department of Medical Genetics, Belfast City Hospital Trust, Lisburn Road, Belfast, BT9 7AD UK
SO Multiple Sclerosis, (April, 1999) Vol. 5, No. 2, pp. 105-109. ISSN: 1352-4585.
DT Article
LA English
SL English

L18 ANSWER 7 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:388670 BIOSIS
DN PREV199799687873
TI TGF-beta-2 **knockout** mice have multiple developmental defects that are non-overlapping with other TGF-beta **knockout** phenotypes.
AU Sanford, L. Phillip; Ormsby, Llona; Gittenberger-De Groot, Adriana C.; Sariola, Hannu; Friedman, Rick; Boivin, Gregory P.; Cardell, Emmma Lou; Doetschman, Thomas (1)
CS (1) Dep. Mol. Genet. Biochem. Microbiol., Univ. Cincinnati, Cincinnati, OH
45267 USA
SO Development (Cambridge), (1997) Vol. 124, No. 13, pp. 2659-2670. ISSN: 0950-1991.
DT Article
LA English

L18 ANSWER 8 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 2000:874978 SCISEARCH
GA The Genuine Article (R) Number: 351BR
TI Cardiovascular malformations in **transforming growth factor-beta 2 knockout** mice relate to altered apoptosis and myocardial and endocardial cushion differentiation
AU Bartram U (Reprint); Doetschmann T; Speer C P; Poelmann R E; GittenbergerdeGroot A C
CS LEIDEN UNIV, DEPT ANAT & EMBRYOL, LEIDEN, NETHERLANDS; UNIV CINCINNATI, DEPT CELL BIOL NEUROBIOL & ANAT, CINCINNATI, OH 45221; UNIV CHILDRENS HOSP, WURZBURG, GERMANY
CYA NETHERLANDS; USA; GERMANY
SO EUROPEAN HEART JOURNAL, (AUG-SEP 2000) Vol. 21, Supp. [S], pp. 3388-3388.
Publisher: W B SAUNDERS CO LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND.

ISSN: 0195-668X.
DT Conference; Journal
FS CLIN
LA English
REC Reference Count: 0

L18 ANSWER 9 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 2000:577755 SCISEARCH
GA The Genuine Article (R) Number: 337DZ
TI The expression and structure of TGF-beta 2 transcripts in rat muscles
AU Koishi K (Reprint); Dalzell K G B; McLennan I S
CS UNIV OTAGO, SCH MED SCI, DEPT ANAT & STRUCT BIOL, POB 913, DUNEDIN, NEW ZEALAND (Reprint)
CYA NEW ZEALAND
SO BIOCHIMICA ET BIOPHYSICA ACTA-GENE STRUCTURE AND EXPRESSION, (24 JUL 2000)
Vol. 1492, No. 2-3, pp. 311-319.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0167-4781.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 56
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L18 ANSWER 10 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 2000:568689 SCISEARCH
GA The Genuine Article (R) Number: 336LN
TI Delayed wound healing in immunodeficient TGF-beta 1 **knockout** mice
AU Crowe M J; Doetschman T (Reprint); Greenhalgh D G
CS UNIV CINCINNATI, COLL MED, DEPT MOL GENET BIOCHEM & MICROBIOL, 231 BETHESDA AVE ML 524, CINCINNATI, OH 45267 (Reprint); UNIV CINCINNATI, COLL MED, DEPT MOL GENET BIOCHEM & MICROBIOL, CINCINNATI, OH 45267; UNIV CINCINNATI, COLL MED, DEPT SURG, CINCINNATI, OH 45267; SHRINERS HOSP CHILDREN, CINCINNATI, OH; UNIV CALIF DAVIS, DEPT SURG, DAVIS, CA 95616
CYA USA
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, (JUL 2000) Vol. 115, No. 1, pp. 3-11.
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148.
ISSN: 0022-202X.
DT Article; Journal
FS LIFE; CLIN
LA English
REC Reference Count: 53
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L18 ANSWER 11 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1999:616726 SCISEARCH
GA The Genuine Article (R) Number: 223MH
TI Characterization of GDF-10 expression patterns and null mice
AU Zhao R B; Lawler A M; Lee S J (Reprint)
CS JOHNS HOPKINS UNIV, SCH MED, DEPT MOL BIOL & GENET, BALTIMORE, MD 21205 (Reprint); JOHNS HOPKINS UNIV, SCH MED, DEPT MOL BIOL & GENET, BALTIMORE, MD 21205; JOHNS HOPKINS UNIV, SCH MED, DEPT GYNECOL & OBSTET, BALTIMORE, MD 21205

CYA USA
SO DEVELOPMENTAL BIOLOGY, (1 AUG 1999) Vol. 212, No. 1, pp. 68-79.
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495.
ISSN: 0012-1606.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 37
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L18 ANSWER 12 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 97:536201 SCISEARCH
GA The Genuine Article (R) Number: XK191
TI TGF beta 2 **knockout** mice have multiple developmental defects that are nonoverlapping with other TGF beta **knockout** phenotypes
AU Sanford L P; Ormsby I; GittenbergerdeGroot A C; Sariola H; Friedman R; Boivin G P; Cardell E L; Doetschman T (Reprint)
CS UNIV CINCINNATI, DEPT MOL GENET BIOCHEM & MICROBIOL, CINCINNATI, OH 45267 (Reprint); UNIV CINCINNATI, DEPT MOL GENET BIOCHEM & MICROBIOL, CINCINNATI, OH 45267; UNIV CINCINNATI, DEPT OTOLARYNGOL, CINCINNATI, OH 45267; UNIV CINCINNATI, DEPT PATHOL & LAB MED, CINCINNATI, OH 45267; UNIV CINCINNATI, DEPT CELL BIOL NEUROBIOL & ANAT, CINCINNATI, OH 45267; UNIV HELSINKI, INST BIOTECHNOL, HELSINKI, FINLAND; LEIDEN UNIV, DEPT ANAT, LEIDEN, NETHERLANDS
CYA USA; FINLAND; NETHERLANDS
SO DEVELOPMENT, (JUL 1997) Vol. 124, No. 13, pp. 2659-2670.
Publisher: COMPANY OF BIOLOGISTS LTD, BIDDER BUILDING CAMBRIDGE COMMERCIAL PARK COWLEY RD, CAMBRIDGE, CAMBS, ENGLAND CB4 4DL.
ISSN: 0950-1991.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 76
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L18 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 2000:521293 CAPLUS
DN 133:188394
TI Delayed wound healing in immunodeficient TGF-.beta.1 **knockout** mice
AU Crowe, Maria J.; Doetschman, Thomas; Greenhalgh, David G.
CS Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, 45267-0524, USA
SO J. Invest. Dermatol. (2000), 115(1), 3-11
CODEN: JIDEAE; ISSN: 0022-202X
PB Blackwell Science, Inc.
DT Journal
LA English
RE.CNT 20
RE
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(4) Sanford, L; Dev 1997, V124, P2659 CAPLUS
(5) Schwartzman, R; Endocr Rev 1993, V14, P133 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 2000:184242 CAPLUS
DN 132:304474
TI Acute hepatotoxicant exposure induces TNFR-mediated hepatic injury and cytokine/apoptotic gene expression
AU Horn, Thomas L.; O'Brien, Timothy D.; Schook, Lawrence B.; Rutherford, Mark S.
CS Toxicology Graduate Program, Department of Veterinary PathoBiology, University of Minnesota, St. Paul, MN, 55108, USA
SO Toxicol. Sci. (2000), 54(1), 262-273
CODEN: TOSCF2; ISSN: 1096-6080
PB Oxford University Press
DT Journal
LA English
RE.CNT 56
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(3) Blazka, M; Toxicol Appl Pharmacol 1995, V133, P43 CAPLUS
(4) Blazka, M; Toxicol Pathol 1996, V24, P181 CAPLUS
(5) Boess, F; Hepatology 1998, V27, P1021 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 1999:637151 CAPLUS
DN 131:332527
TI Pathogenesis of cleft palate in TGF-.beta.3 **knockout** mice
AU Taya, Yuji; O'Kane, Sharon; Ferguson, Mark W. J.
CS Division of Cells, Immunology and Development, School of Biological Sciences, The University of Manchester, Manchester, M13 9PT, UK
SO Development (Cambridge, U. K.) (1999), 126(17), 3869-3879
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
RE.CNT 52
RE
(1) Brunet, C; Int J Dev Biol 1995, V39, P345 CAPLUS
(4) Ellis, I; Cytokine 1998, V10, P281 CAPLUS
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(13) Gumbiner, B; Cell 1996, V84, P345 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 1999:318514 CAPLUS
DN 131:128920
TI Lack of association of transforming growth factor (TGF)-.beta.1 and .beta.2 gene polymorphisms with multiple sclerosis (MS) in Northern Ireland
AU McDonnell, G. V.; Kirk, C. W.; Hawkins, S. A.; Graham, C. A.
CS Northern Ireland Regional Neurology Service, Royal Victoria Hospital, Belfast, UK
SO Mult. Scler. (1999), 5(2), 105-109
CODEN: MUSCFZ; ISSN: 1352-4585
PB Stockton Press
DT Journal

LA English
RE.CNT 36
RE
(1) Beck, J; Acta Neurol Scand 1991, V84, P452 CAPLUS
(4) Ebers, G; Nat Genet 1996, V13, P472 CAPLUS
(5) Fukaura, H; J Clin Invest 1996, V98, P70 CAPLUS
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(8) Gyapay, G; Nat Genet 1994, V7, P246 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 1999:52076 CAPLUS
DN 130:262560
TI The role of TGF.beta.1 in initiating hepatic stellate cell activation in vivo
AU Hellerbrand, Claus; Stefanovic, Branko; Giordano, Frank; Burchardt, Elmar R.; Brenner, David A.
CS Departments of Medicine and Biochemistry and Biophysics, University of North Carolina, Chapel Hill, NC, 27599-7080, USA
SO J. Hepatol. (1999), 30(1), 77-87
CODEN: JOHEEC; ISSN: 0168-8278
PB Munksgaard International Publishers Ltd.
DT Journal
LA English
RE.CNT 68
RE
(2) Bachem, M; J Clin Invest 1992, V89, P19 CAPLUS
(3) Bedossa, P; J Hepatol 1995, V22, P37 CAPLUS
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(6) Britton, R; Hepatogastroenterology 1994, V41, P343 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 1997:462877 CAPLUS
DN 127:171823
TI TGF.beta.2 **knockout** mice have multiple developmental defects that are non-overlapping with other TGF.beta. **knockout** phenotypes
AU Sanford, L. Philip; Ormsby, Ilona; Gittenberger-de Groot, Adriana C.; Sariola, Hannu; Friedman, Rick; Boivin, Gregory P.; Cardell, Emma Lou; Doetschman, Thomas
CS Departments of Molecular Genetics, Biochemistry and Microbiology, University of Cincinnati, Cincinnati, OH, 45267, USA
SO Development (Cambridge, U. K.) (1997), 124(13), 2659-2670
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists
DT Journal
LA English

L18 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 1997:147263 CAPLUS
DN 126:210210
TI Involvement of the TNF-.alpha. system and the Fas system in the induction of apoptosis of mouse mammary glands after weaning
AU Kojima, H.; Fukazawa, Y.; Sato, T.; Enari, M.; Tomooka, Y.; Matsuzawa, A.;
Ohta, Y.; Iguchi, T.

CS Graduate School of Integrated Science, Yokohama City University, Yokohama,
236, Japan
SO Apoptosis (1996), 1(3), 201-208
CODEN: APOPFN; ISSN: 1360-8185
PB Rapid Science Publishers
DT Journal
LA English

=>

---Logging off of STN---

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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Sep 29  The Philippines Inventory of Chemicals and Chemical
                  Substances (PICCS) has been added to CHEMLIST
 NEWS  3  Oct 27  New Extraction Code PAX now available in Derwent
                  Files
 NEWS  4  Oct 27  SET ABBREVIATIONS and SET PLURALS extended in
                  Derwent World Patents Index files
 NEWS  5  Oct 27  Patent Assignee Code Dictionary now available
                  in Derwent Patent Files
 NEWS  6  Oct 27  Plasdoc Key Serials Dictionary and Echoing added to
                  Derwent Subscriber Files WPIDS and WPIX
 NEWS  7  Nov 29  Derwent announces further increase in updates for DWPI
 NEWS  8  Dec  5  French Multi-Disciplinary Database PASCAL Now on STN
 NEWS  9  Dec  5  Trademarks on STN - New DEMAS and EUMAS Files
 NEWS 10  Dec 15  2001 STN Pricing
 NEWS 11  Dec 17  Merged CEABA-VTB for chemical engineering and
                  biotechnology
 NEWS 12  Dec 17  Corrosion Abstracts on STN
 NEWS 13  Dec 17  SYNTHLINE from Prous Science now available on STN
 NEWS 14  Dec 17  The CA Lexicon available in the CAPLUS and CA files
 NEWS 15  Jan 05  AIDSLINE is being removed from STN
 NEWS 16  Feb 06  Engineering Information Encompass files have new names
 NEWS 17  Feb 16  TOXLINE no longer being updated

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FILE 'HOME' ENTERED AT 11:16:33 ON 19 FEB 2001

=> file medline embase biosis scisearch caplus
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COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION
FULL ESTIMATED COST | 0.15 | 0.15

FILE 'MEDLINE' ENTERED AT 11:16:57 ON 19 FEB 2001

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=> s TGF beta

L1 68514 TGF BETA

=> s l1 and 2

L2 27819 L1 AND 2

=> s l2 and sperm antigen

L3 1 L2 AND SPERM ANTIGEN

=> d l3 all

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
AN 1998:618828 CAPLUS
DN 129:212101
TI Treatment and diagnosis of infertility using **TGF.beta.** or activin
IN Robertson, Sarah Anne; Tremellen, Kelton Paul
PA Luminis Pty. Ltd., Australia
SO PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-18
ICS A61K039-00; G01N033-68
CC 2-3 (Mammalian Hormones)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9839021	A1	19980911	WO 1998-AU149	19980306
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9862846	A1	19980922	AU 1998-62846	19980306
	AU 722150	B2	20000720		

EP 1028743 A1 20000823 EP 1998-906749 19980306
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI
PRAI AU 1997-5508 19970306
WO 1998-AU149 19980306

AB A method of treating an infertility condition in humans or mammals, by exposure of a prospective mother to **TGF.beta.** or a deriv. or analog of **TGF.beta.**. The exposure is advantageously in conjunction with one or more antigens of a prospective father so that a hyporesponsive immune reaction is mounted to the one or more antigens of the prospective father. The treatment illicts a transient hyporesponsive immune reaction that alleviates symptoms of the infertility condition. Methods are also claimed for diagnosing an infertility condition in males by testing the level of **TGF.beta.** in the seminal fluid and in females by testing for the capacity of the female to convert the inactive form of **TGF.beta.** to the active form. Some specific disorders or procedures that may benefit from the present invention are: recurrent miscarriage, IVF treatment, anti-sperm antibody therapy, pre-eclampsia and intra-uterine growth restriction, prospective anal. of stud animal fertility in livestock breeding industries, and optimization of pregnancy outcome in livestock breeding industries.

ST infertility treatment diagnosis TGFbeta activin; paternal antigen TGFbeta infertility treatment diagnosis

IT Platelet (blood)
(**TGF.beta.** administration in the form of platelets; treatment and diagnosis of infertility using **TGF.beta.** or activin in conjunction with one or more antigens of a prospective father)

IT Antibodies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anti-sperm antibody therapy; treatment and diagnosis of infertility using **TGF.beta.** or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Semen
Seminal plasma
(antigen administration in; treatment and diagnosis of infertility using **TGF.beta.** or activin in conjunction with one or more antigens of a prospective father)

IT Leukocyte
Sperm
(**antigen** administration on; treatment and diagnosis of infertility using **TGF.beta.** or activin in conjunction with one or more antigens of a prospective father)

IT Livestock
(breeding; treatment and diagnosis of infertility using **TGF.beta.** or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs. or analogs; treatment and diagnosis of infertility using **TGF.beta.** or activin in conjunction with one or more antigens of a prospective father)

IT Uterine diseases
(intra-uterine growth restriction; treatment and diagnosis of infertility using **TGF.beta.** or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Breeding (animal)
(livestock; treatment and diagnosis of infertility using **TGF.beta.** or activin in conjunction with one or more antigens of a

prospective father to benefit various disorders and procedures)
IT Diagnosis
Infertility (animal)
(treatment and diagnosis of infertility using **TGF**
.beta. or activin in conjunction with one or more antigens of a
prospective father)
IT Antigens
Class I MHC antigens
MHC antigens
Transforming growth factor .beta.1
Transforming growth factor .beta.**2**
Transforming growth factor .beta.3
Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); THU
(Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment and diagnosis of infertility using **TGF**
.beta. or activin in conjunction with one or more antigens of a
prospective father)
IT Abortion (spontaneous)
In vitro fertilization (animal)
Preeclampsia
(treatment and diagnosis of infertility using **TGF**
.beta. or activin in conjunction with one or more antigens of a
prospective father to benefit various disorders and procedures)
IT Drug delivery systems
Vaginal drug delivery systems
(treatment and diagnosis of infertility using compns. contg.
TGF.beta. or activin in conjunction with one or more
antigens of a prospective father)

=> d his

(FILE 'HOME' ENTERED AT 11:16:33 ON 19 FEB 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:16:57 ON
19 FEB 2001
L1 68514 S TGF BETA
L2 27819 S L1 AND 2
L3 1 S L2 AND SPERM ANTIGEN

=> s l2 and immune tolerance

L4 165 L2 AND IMMUNE TOLERANCE

=> s l4 and implantation

L5 1 L4 AND IMPLANTATION

=> d l5 all

L5 ANSWER 1 OF 1 MEDLINE
AN 93252646 MEDLINE
DN 93252646
TI Transforming growth factor-beta (**TGF-beta**)-mediated
immunosuppression in the tumor-bearing state: enhanced production of
TGF-beta and a progressive increase in **TGF-**
beta susceptibility of anti-tumor CD4+ T cell function.
AU Li X F; Takiuchi H; Zou J P; Katagiri T; Yamamoto N; Nagata T; Ono S;
Fujiwara H; Hamaoka T
CS Biomedical Research Center, Osaka University Medical School.

SO JAPANESE JOURNAL OF CANCER RESEARCH, (1993 Mar) 84 (3) 315-25.
Journal code: HBA. ISSN: 0910-5050.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199308
AB The present study deals with the effect of transforming growth factor-beta (**TGF-beta**) on anti-tumor immune responsiveness at various stages of the tumor-bearing state. Spleen cells from BALB/c mice bearing a syngeneic tumor (CSA1M) 1-3 wk after inoculation with CSA1M cells produced interleukin-**2** (IL-**2**) and macrophage-activating factor (MAF)/interferon-gamma (IFN-gamma) upon in vitro culture without addition of exogenous tumor antigens. This lymphokine production was achieved through collaboration between anti-CSA1M CD4+ T cells and antigen-presenting cells that had been pulsed with CSA1M tumor antigens in vivo in the tumor-bearing state. The IL-**2**-producing capacity of CD4+ T cells reached the maximal level as early as one week after tumor **implantation** but decreased with the progress of tumor-bearing stages. In contrast, the capacity of CD4+ T cells to produce MAF/IFN-gamma was not affected but was maintained at high levels even late in the tumor-bearing state. The addition of recombinant **TGF-beta** (rTGF-beta) to cultures of spleen cells from various tumor-bearing stages resulted in the suppression of lymphokine production. However, the magnitude of the **TGF-beta**-induced suppression varied depending on which tumor-bearing stages of splenic cells were tested as a responding cell population; it was slight in cells from early (1-3 wk) tumor-bearing stages but increased in cells from donor mice at later tumor-bearing stages. Thus, spleen cells from late tumor-bearing stages with weak but significant IL-**2**-producing and considerable MAF/IFN-gamma producing capacities failed to produce these lymphokines when rTGF-beta was present in cultures. A progressive increase in the **TGF-beta** susceptibility was also observed for IL-4-producing Th2 as well as IL-**2**/MAF-producing Th1 cells. In addition, increased levels of **TGF-beta** were detected in plasma from tumor-bearing mice at late stages. Taken together, these results indicate that tumor-bearing mice exhibit enhanced production of **TGF-beta** as well as a progressive increase in the susceptibility of anti-tumor CD4+ T cells to **TGF-beta**-induced suppressive mechanisms.
CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Cell Division: IM, immunology
Cells, Cultured
*CD4-Positive T-Lymphocytes: IM, immunology
Dose-Response Relationship, Drug
*Fibrosarcoma: IM, immunology
***Immune Tolerance: DE, drug effects**
Interferon Type II: BI, biosynthesis
Interleukin-2: BI, biosynthesis
Interleukin-4: BI, biosynthesis
Macrophage-Activating Factors: BI, biosynthesis
Mice
Mice, Inbred BALB C
Spleen: IM, immunology
T-Lymphocytes, Cytotoxic: PH, physiology
T-Lymphocytes, Helper-Inducer: IM, immunology
Time Factors
Transforming Growth Factor beta: BI, biosynthesis
*Transforming Growth Factor beta: PD, pharmacology
Tumor Cells, Cultured
RN 82115-62-6 (Interferon Type II)

CN 0 (Interleukin-2); 0 (Interleukin-4); 0 (Macrophage-Activating Factors); 0 (Transforming Growth Factor beta)

=> s Transforming growth factor beta-2

L6 3106 TRANSFORMING GROWTH FACTOR BETA-2

=> s l6 and maternal immune tolerance

L7 0 L6 AND MATERNAL IMMUNE TOLERANCE

=> s l6 and fertility

L8 2 L6 AND FERTILITY

=> d l8 all 1-2

L8 ANSWER 1 OF 2 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1998:920054 SCISEARCH
GA The Genuine Article (R) Number: 142QY
TI The bone morphogenetic protein 15 gene is X-linked and expressed in oocytes
AU Dube J L; Wang P; Elvin J; Lyons K M; Celeste A J; Matzuk M M (Reprint)
CS BAYLOR COLL MED, DEPT PATHOL, 1 BAYLOR PLAZA, HOUSTON, TX 77030 (Reprint);
BAYLOR COLL MED, DEPT PATHOL, HOUSTON, TX 77030; BAYLOR COLL MED, DEPT CELL BIOL, HOUSTON, TX 77030; BAYLOR COLL MED, DEPT HUMAN MOL GENET, HOUSTON, TX 77030; GENET INST INC, DEPT TISSUE GROWTH & REPAIR, CAMBRIDGE,
MA 02140; UNIV CALIF LOS ANGELES, SCH MED, DEPT ORTHOPAED SURG, LOS ANGELES, CA 90095; UNIV CALIF LOS ANGELES, SCH MED, DEPT BIOL CHEM, LOS ANGELES, CA 90095
CYA USA
SO MOLECULAR ENDOCRINOLOGY, (DEC 1998) Vol. 12, No. 12, pp. 1809-1817.
Publisher: ENDOCRINE SOC, 4350 EAST WEST HIGHWAY SUITE 500, BETHESDA, MD 20814-4110.
ISSN: 0888-8809.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 35
AB We have taken advantage of the sequence relationships among the bone morphogenetic proteins (BMPs) to identify the mouse Bmp15 and human BMP15 genes. The 392-amino acid prepropeptides encoded by these BMP genes exhibit significant homology to each other, although the 70% identity observed between the 125-amino acid mature peptides is considerably lower than that seen in comparisons of other mouse and human orthologs. Both genes share a common structural organization and encode mature peptides that lack the cysteine residue normally involved in the formation of a covalent dimer. In addition, mouse Bmp15 and human BMP15 map to conserved syntenic regions on the X chromosome. We demonstrate, through a combination of Northern blot and in situ hybridization analyses, that mouse Bmp15 is expressed specifically in the oocyte beginning at the one-layer primary follicle stage and continuing through ovulation. Interestingly, BMP-15 is most closely related to and shares a coincident expression pattern with the mouse growth/differentiation factor 9 (GDF-9) gene that is essential for female **fertility**. Our findings will be important for defining the role of BMP-15 in follicular development.
CC ENDOCRINOLOGY & METABOLISM
STP KeyWords Plus (R): GROWTH-FACTOR-BETA; HUMAN OSTEOGENIC PROTEIN-1; **TRANSFORMING GROWTH-FACTOR-BETA-**

2; CRYSTAL-STRUCTURE; IN-VIVO; SUPERFAMILY; MEMBERS; FAMILY; MOUSE; HYBRIDIZATION

RE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
ALBRECHT U	1997		23	MOL CELLULAR METHODS
AONO A	1995	210	670	BIOCHEM BIOPH RES CO
BALDINI A	1992	14	181	GENOMICS
BEHRINGER R R	1994	79	415	CELL
BOYD Y	1997	7	313	MAMM GENOME
CELESTE A J	1990	87	9843	P NATL ACAD SCI USA
CHEIFETZ S	1988	263	10783	J BIOL CHEM
DAOPIN S	1992	257	369	SCIENCE
DONG L W	1996	9	383	J MOL RECOGNIT
DUDLEY A T	1995	9	2795	GENE DEV
GRIFFITH D L	1996	93	878	P NATL ACAD SCI USA
HOGAN B L M	1996	10	1580	GENE DEV
ISRAEL D I	1996	13	291	GROWTH FACTORS
JONES C M	1992	6	1961	MOL ENDOCRINOL
KINGSLEY D M	1992	71	399	CELL
KINGSLEY D M	1994	8	133	GENE DEV
KUSUMOTO K	1997	239	575	BIOCHEM BIOPH RES CO
LAU A L	1997		220	INHIBIN ACTIVIN FOLL
MAHMOUDI M	1989	7	331	BIOTECHNIQUES
MATHER J P	1997	215	209	P SOC EXP BIOL MED
MCGRATH S A	1995	9	131	MOL ENDOCRINOL
MCPHERRON A C	1993	268	3444	J BIOL CHEM
OZKAYNAK E	1992	267	25220	J BIOL CHEM
PEDERSEN T	1968	17	555	J REPROD FERTIL
ROSEN V	1996		661	PRINCIPLES BONE BIOL
ROWE L B	1994	5	253	MAMM GENOME
SAMPATH T K	1992	267	20352	J BIOL CHEM
SCHLUNEGGER M P	1993	231	445	J MOL BIOL
TATUSOV R L	1997	278	631	SCIENCE
WANG E A	1990	87	2220	P NATL ACAD SCI USA
WINNIER G	1995	9	2105	GENE DEV
WOLFMAN N M	1997	100	321	J CLIN INVEST
ZHANG H B	1996	122	2977	DEVELOPMENT
ZHAO G Q	1998	125	1103	DEVELOPMENT
ZHAO G Q	1996	10	1657	GENE DEV

L8 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AN 1998:618828 CAPLUS
DN 129:212101
TI Treatment and diagnosis of infertility using TGF.beta. or activin
IN Robertson, Sarah Anne; Tremellen, Kelton Paul
PA Luminis Pty. Ltd., Australia
SO PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-18
ICS A61K039-00; G01N033-68
CC 2-3 (Mammalian Hormones)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9839021	A1	19980911	WO 1998-AU149	19980306

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,

UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9862846 A1 19980922 AU 1998-62846 19980306
AU 722150 B2 20000720
EP 1028743 A1 20000823 EP 1998-906749 19980306
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

PRAI AU 1997-5508 19970306
WO 1998-AU149 19980306

AB A method of treating an infertility condition in humans or mammals, by exposure of a prospective mother to TGF.beta. or a deriv. or analog of TGF.beta.. The exposure is advantageously in conjunction with one or more antigens of a prospective father so that a hyporesponsive immune reaction is mounted to the one or more antigens of the prospective father. The treatment illicts a transient hyporesponsive immune reaction that alleviates symptoms of the infertility condition. Methods are also claimed for diagnosing an infertility condition in males by testing the level of TGF.beta. in the seminal fluid and in females by testing for the capacity of the female to convert the inactive form of TGF.beta. to the active form. Some specific disorders or procedures that may benefit from the present invention are: recurrent miscarriage, IVF treatment, anti-sperm antibody therapy, pre-eclampsia and intra-uterine growth restriction, prospective anal. of stud animal **fertility** in livestock breeding industries, and optimization of pregnancy outcome in livestock breeding industries.

ST infertility treatment diagnosis TGFbeta activin; paternal antigen TGFbeta infertility treatment diagnosis

IT Platelet (blood)
(TGF.beta. administration in the form of platelets; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

IT Antibodies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anti-sperm antibody therapy; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Semen
Seminal plasma
(antigen administration in; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

IT Leukocyte
Sperm
(antigen administration on; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

IT Livestock
(breeding; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs. or analogs; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

IT Uterine diseases
(intra-uterine growth restriction; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more

antigens of a prospective father to benefit various disorders and procedures)

IT Breeding (animal)
(livestock; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Diagnosis
Infertility (animal)
(treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

IT Antigens
Class I MHC antigens
MHC antigens
Transforming growth factor .beta.1
Transforming growth factor .beta.
2
Transforming growth factor .beta.3
Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

IT Abortion (spontaneous)
In vitro fertilization (animal)
Preeclampsia
(treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Drug delivery systems
Vaginal drug delivery systems
(treatment and diagnosis of infertility using compns. contg. TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

=> s transforming growth factor.beta.2

L9 3106 TRANSFORMING GROWTH FACTOR.BETA.2

=> s l9 and seminal plasma

L10 2 L9 AND SEMINAL PLASMA

=> d l10 all 1-2

L10 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:373527 BIOSIS
DN PREV199900373527
TI A sensitive and specific in vitro bioassay for activin using a mouse plasmacytoma cell line, MPC-11.
AU Phillips, D. J. (1); Brauman, J. N.; Mason, A. J.; de Kretser, D. M.; Hedger, M. P.
CS (1) Monash Medical Centre, Institute of Reproduction and Development, 246 Clayton Road, Level 3, Block E, Clayton, VIC, 3168 Australia
SO Journal of Endocrinology, (July, 1999) Vol. 162, No. 1, pp. 111-116. ISSN: 0022-0795.
DT Article
LA English
SL English
AB A new in vitro bioassay for activin was developed using the mouse plasmacytoma cell line, MPC-11. Human recombinant (hr) activin A dose-dependently inhibited the proliferation of these cells, whereas a

range of other factors, including inhibin, follistatin and transforming growth factor-beta1, -beta2 and -beta3 had no effect. Conditioned medium containing activin B induced an inhibition similar to hr-activin A. The inhibitory influence of activin A could be blocked by follistatin, but not by hr-inhibin A. This bioassay had a sensitivity for activin A of around 0.4 ng/ml, an ED50 response of 3.5 ng/ml, and an intraassay coefficient of variation of <11%. It offers substantial advantages over existing in vitro activin bioassays in terms of ease of use, specificity and throughput. The utility of the MPC-11 bioassay was demonstrated in the purification of activin from amniotic fluid, where an almost identical profile of bioactive activin A was detected compared with the pituitary cell bioassayof activin. Bioactive activin could also be detected in unpurified ovine allantoic and amniotic fluids and bovine follicular fluid. Measuring activin in untreated and heat-treated human sera or **seminal plasma** was hampered by a non-specific inhibitory effect, so that several serum samples did not run parallel with the hr-activin A standard. This inhibitory effect by serum could not be overcome by addition of follistatin, suggesting it is not activin-like bioactivity. This new bioassay for activin demonstrates widespread applicability for monitoring of purified or partially purified samples during purification procedures, bioactivity measurements, receptor-binding studies and assays of cell culture medium.

CC Endocrine System - General *17002
Developmental Biology - Embryology - General and Descriptive *25502
BC Muridae 86375
IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Methods and Techniques
IT Parts, Structures, & Systems of Organisms
amniotic fluid: embryonic structure
IT Chemicals & Biochemicals
activin; follistatin; inhibin; recombinant activin; transforming growth factor-beta 1; **transforming growth factor -beta 2**; transforming growth factor-beta 3
IT Methods & Equipment
in vitro bioassay: analytical method
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
MPC-11 cell line (Muridae): plasmacytoma cell
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 57285-09-3 (INHIBIN)
117628-82-7 (FOLLISTATIN)

L10 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AN 1998:618828 CAPLUS
DN 129:212101
TI Treatment and diagnosis of infertility using TGF.beta. or activin
IN Robertson, Sarah Anne; Tremellen, Kelton Paul
PA Luminis Pty. Ltd., Australia
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DT Patent

LA English
IC ICM A61K038-18
ICS A61K039-00; G01N033-68
CC 2-3 (Mammalian Hormones)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9839021	A1	19980911	WO 1998-AU149	19980306
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9862846	A1	19980922	AU 1998-62846	19980306
AU 722150	B2	20000720		
EP 1028743	A1	20000823	EP 1998-906749	19980306
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI AU 1997-5508 19970306
WO 1998-AU149 19980306

AB A method of treating an infertility condition in humans or mammals, by exposure of a prospective mother to TGF.beta. or a deriv. or analog of TGF.beta.. The exposure is advantageously in conjunction with one or more antigens of a prospective father so that a hyporesponsive immune reaction is mounted to the one or more antigens of the prospective father. The treatment illicts a transient hyporesponsive immune reaction that alleviates symptoms of the infertility condition. Methods are also claimed for diagnosing an infertility condition in males by testing the level of TGF.beta. in the seminal fluid and in females by testing for the capacity of the female to convert the inactive form of TGF.beta. to the active form. Some specific disorders or procedures that may benefit from the present invention are: recurrent miscarriage, IVF treatment, anti-sperm antibody therapy, pre-eclampsia and intra-uterine growth restriction, prospective anal. of stud animal fertility in livestock breeding industries, and optimization of pregnancy outcome in livestock breeding industries.

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Seminal plasma
(antigen administration in; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

IT Leukocyte
Sperm
(antigen administration on; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

IT Livestock

(breeding; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(derivs. or analogs; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

IT Uterine diseases
(intra-uterine growth restriction; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Breeding (animal)
(livestock; treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Diagnosis
Infertility (animal)
(treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

IT Antigens
Class I MHC antigens
MHC antigens
Transforming growth factor .beta.1
Transforming growth factor .beta.
2
Transforming growth factor .beta.3
Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

IT Abortion (spontaneous)
In vitro fertilization (animal)
Preeclampsia
(treatment and diagnosis of infertility using TGF.beta. or activin in conjunction with one or more antigens of a prospective father to benefit various disorders and procedures)

IT Drug delivery systems
Vaginal drug delivery systems
(treatment and diagnosis of infertility using compns. contg. TGF.beta. or activin in conjunction with one or more antigens of a prospective father)

=> d his

(FILE 'HOME' ENTERED AT 11:16:33 ON 19 FEB 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:16:57 ON 19 FEB 2001

L1	68514	S	TGF BETA
L2	27819	S	L1 AND 2
L3	1	S	L2 AND SPERM ANTIGEN
L4	165	S	L2 AND IMMUNE TOLERANCE
L5	1	S	L4 AND IMPLANTATION
L6	3106	S	TRANSFORMING GROWTH FACTOR BETA-2
L7	0	S	L6 AND MATERNAL IMMUNE TOLERANCE
L8	2	S	L6 AND FERTILITY
L9	3106	S	TRANSFORMING GROWTH FACTOR.BETA.2

L10 2 S L9 AND SEMINAL PLASMA

=> s l9 and trophoblast

L11 37 L9 AND TROPHOBLAST

=> s l11 and fibronectin

L12 3 L11 AND FIBRONECTIN

=> d l12

L12 ANSWER 1 OF 3 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:192912 BIOSIS
DN PREV199799492115
TI Expression of TGF-beta and extracellular matrix proteins at the fetomaternal interface of developing placentas in first trimester.
AU Nemoto, N. (1); Hayakawa, S.; Chishima, F.; Kinukawa, N.; Sakurai, I.; Segi, K.; Satoh, K.
CS (1) Dep. Pathol., Nihon Univ. Sch. Med., Tokyo 173 Japan
SO Pathology International, (1996) Vol. 46, No. SUPPL. 1, pp. 681.
Meeting Info.: XXI International Congress of the International Academy of Pathology and 12th World Congress of Academic and Environmental Pathology Budapest, Hungary October 20-25, 1996
ISSN: 1320-5463.
DT Conference; Abstract; Conference
LA English

=> d l12 all 1-3

L12 ANSWER 1 OF 3 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:192912 BIOSIS
DN PREV199799492115
TI Expression of TGF-beta and extracellular matrix proteins at the fetomaternal interface of developing placentas in first trimester.
AU Nemoto, N. (1); Hayakawa, S.; Chishima, F.; Kinukawa, N.; Sakurai, I.; Segi, K.; Satoh, K.
CS (1) Dep. Pathol., Nihon Univ. Sch. Med., Tokyo 173 Japan
SO Pathology International, (1996) Vol. 46, No. SUPPL. 1, pp. 681.
Meeting Info.: XXI International Congress of the International Academy of Pathology and 12th World Congress of Academic and Environmental Pathology Budapest, Hungary October 20-25, 1996
ISSN: 1320-5463.
DT Conference; Abstract; Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Cytology and Cytochemistry - Human *02508
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Anatomy and Histology, General and Comparative - Microscopic and Ultramicroscopic Anatomy *11108
Metabolism - Proteins, Peptides and Amino Acids *13012
Reproductive System - Anatomy *16502
Reproductive System - Physiology and Biochemistry *16504
Reproductive System - Pathology *16506
Endocrine System - General *17002
Developmental Biology - Embryology - General and Descriptive *25502
Developmental Biology - Embryology - Pathological *25503

Developmental Biology - Embryology - Morphogenesis, General *25508
In Vitro Studies, Cellular and Subcellular *32600
Immunology and Immunochemistry - General; Methods *34502
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Development; Endocrine System (Chemical Coordination and Homeostasis); Immune System (Chemical Coordination and Homeostasis); Membranes (Cell Biology); Metabolism; Morphology; Reproductive System (Reproduction)
IT Miscellaneous Descriptors
ABORTION; ADULT; ANALYTICAL METHOD; DEVELOPMENT; EMBRYO; EMBRYONIC STRUCTURE; ENDOCRINE SYSTEM; EXPRESSION; EXTRACELLULAR MATRIX PROTEINS; FEMALE; FETOMATERNAL INTERFACE; FETUS; **FIBRONECTIN**; FIRST TRIMESTER; IMMUNOHISTOCHEMISTRY; IMMUNOLOGIC METHOD; IN-VITRO; PATIENT; PLACENTA; PREGNANCY RELATED DISEASE; REPRODUCTIVE SYSTEM; REPRODUCTIVE SYSTEM DISEASE/FEMALE; TENASCIN; TGF-BETA-1; TGF-BETA-2; TRANSFORMING GROWTH FACTOR-BETA-1; **TRANSFORMING GROWTH FACTOR-BETA-2**; **TROPHOBLAST**; TROPHOBLASTIC GROWTH; TROPHOBLASTIC INVASION; TROPHOBLASTIC MIGRATION
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L12 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2001 ACS
AN 1998:621378 CAPLUS
DN 129:257363
TI Regulation of **trophoblast** invasion and diagnosis of preeclampsia
IN Caniggia, Isabella; Post, Martin; Lye, Stephen
PA Mount Sinai Hospital Corp., Can.; Hospital for Sick Children
SO PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM G01N033-68
ICS G01N033-566; C07K014-47
CC 9-16 (Biochemical Methods)
Section cross-reference(s): 2, 3, 6, 13, 14
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9840747	A1	19980917	WO 1998-CA180	19980305
	W: AU, CA, JP, MX, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9862871	A1	19980929	AU 1998-62871	19980305
	EP 968430	A1	20000105	EP 1998-906777	19980305
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	US 1997-39919		19970307		
	WO 1998-CA180		19980305		

AB Methods are provided for the diagnosis and treatment of patients with increased risk of preeclampsia. The invention describes mechanisms that regulate **trophoblast** invasion. The inventors have found that antisense disruption of the expression of the TGF.beta. receptor, endoglin, triggers invasion of cytotrophoblast from first trimester villous explants in vitro indicating that the TGF.beta. receptor system, and in particular endoglin, plays a crit. role in regulating this process.

Broadly stated the present invention relates to a method for detecting, preventing, and/or treating a condition requiring regulation of **trophoblast** invasion by modulating (a) TGF.beta.3, (b) receptors of cytokines of the TGF.beta. family, (c) HIF-1.alpha., and/or (d) O2 tension. A method is also described for diagnosing increased risk of preeclampsia in a subject comprising detecting TGF.beta.3 or its receptors, or HIF-1.alpha. in a sample from the subject.

ST **trophoblast** invasion pregnancy preeclampsia diagnosis

IT Transcription factors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(HIF-1 (hypoxia-inducible factor 1), alpha; regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Carcinoma inhibitors
(choriocarcinoma; regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Choriocarcinoma
(inhibitors; regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Blood analysis
Choriocarcinoma
Diagnosis
Drug screening
Placenta
Preeclampsia
Pregnancy
Pregnancy disorders
Trophoblast
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Transforming growth factor .beta.3
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Cytokine receptors
Transforming growth factor .beta. receptors
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Antisense DNA
Antisense oligonucleotides
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT **Fibronectins**
Integrin .alpha.5
Transforming growth factor .beta.1
Transforming growth factor .beta.
2
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Endoglins

Transforming growth factor .beta. type I receptors
Transforming growth factor .beta. type II receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Decorins
Fetuins
Thyroglobulin
.alpha.2-Macroglobulins
RL: BPR (Biological process); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT Antibodies
RL: BPR (Biological process); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(to TGF.beta.3; regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT 146480-36-6, Gelatinase B 213322-42-0 213322-45-3 213322-46-4 213322-47-5 213322-48-6 213394-93-5
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

IT 7782-44-7, Oxygen, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(regulation of **trophoblast** invasion and diagnosis of preeclampsia)

L12 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2001 ACS
AN 1997:675833 CAPLUS
DN 127:355610
TI Endoglin regulates **trophoblast** differentiation along the invasive pathway in human placental villous explants
AU Caniggia, Isabella; Taylor, Carolyn V.; Knox Ritchie, J. W.; Lye, Stephen J.; Letarte, Michelle
CS Program Fetal Health and Development, Sanuel Lunenfeld Res. Inst., Univ. Toronto, Toronto, ON, M5G 1X5, Can.
SO Endocrinology (1997), 138(11), 4977-4988
CODEN: ENDOAO; ISSN: 0013-7227
PB Endocrine Society
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB Successful invasion of the maternal vascular system by **trophoblast** cells in a prerequisite for the establishment of a normal hemochorial placenta. Transforming growth factor-.beta. (THF.beta.) has been implicated in the regulation of **trophoblast** invasiveness into the uterus. Endoglin is a component of the TGF.beta. receptor complex that binds .beta.1 and .beta.3 isoforms and is expressed at high levels on syncytiotrophoblast throughout pregnancy and is also transiently up-regulated on extra-villous **trophoblasts** differentiating along the invasive pathway. The authors investigated the role of endoglin in a serum-free human villous explant culture system that allows the study of **trophoblast** outgrowth, migration, and invasion and mimics events occurring in anchoring villi during the first trimester of gestation. Addn. to explant cultures from 5-8 wk gestation of a monoclonal antibody to endoglin or of antisense endoglin oligonucleotides significantly stimulated **trophoblast** outgrowth and migration. These responses were specific, as incubation of explants with nonimmune IgG or sense and

scrambled oligonucleotides had no effect. Antisense endoglin-induced **trophoblast** outgrowth and migration were accompanied by cell division of villous-assocd. **trophoblasts** within the proximal region of the forming column and by the characteristic switch in integrins
obsd. in anchoring villi in situ. Treatment of villous explants with antibody and antisense oligonucleotides to endoglin also resulted in an increased **fibronectin** release into the culture medium. The stimulatory effect of antisense endoglin on **fibronectin** prodn. was overcome by the addn. of exogenous TGF.beta.2, but not TGF.beta.1 and -.beta.3. These findings suggest that endoglin expression in the transition from polarized to nonpolarized **trophoblasts** in anchoring villi is necessary for mediation of the inhibitory effect of TGF.beta.1 and/or TGF.beta.3 on **trophoblast** differentiation along the invasive pathway.

ST endoglin **trophoblast** differentiation invasive pathway; TGF **trophoblast** differentiation placenta endoglin

IT Cell differentiation
Cell division
Cell migration
Trophoblast
Uterus
(endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

IT Transforming growth factor .beta.1
Transforming growth factor .beta.
2
Transforming growth factor .beta.3
Transforming growth factors .beta.
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

IT Integrin .alpha.5
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

IT Keratins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

IT Transforming growth factor .beta. receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

IT **Fibronectins**
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

IT Glycoproteins (specific proteins and subclasses)
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(endoglins; endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

IT Pregnancy
(first trimester; endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

IT Placenta
(villus; endoglin regulates TGF-induced **trophoblast**

differentiation along invasive pathway in human placental villous explants)

IT Integrins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process) (.alpha.6; endoglin regulates TGF-induced **trophoblast** differentiation along invasive pathway in human placental villous explants)

=> d his

(FILE 'HOME' ENTERED AT 11:16:33 ON 19 FEB 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:16:57 ON 19 FEB 2001

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L1        68514 S TGF BETA
L2        27819 S L1 AND 2
L3            1 S L2 AND SPERM ANTIGEN
L4          165 S L2 AND IMMUNE TOLERANCE
L5            1 S L4 AND IMPLANTATION
L6         3106 S TRANSFORMING GROWTH FACTOR BETA-2
L7            0 S L6 AND MATERNAL IMMUNE TOLERANCE
L8            2 S L6 AND FERTILITY
L9         3106 S TRANSFORMING GROWTH FACTOR.BETA.2
L10           2 S L9 AND SEMINAL PLASMA
L11          37 S L9 AND TROPHOBLAST
L12           3 S L11 AND FIBRONECTIN
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=> s l11 and tropho ulteronectin

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L13           0 L11 AND TROPHO ULTERONECTIN
```

=> s l11 and uteronectin

```
L14           0 L11 AND UTERONECTIN
```

=> s l11 and tropho-uteronectin

```
L15           0 L11 AND TROPHO-UTERONECTIN
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=> d his

(FILE 'HOME' ENTERED AT 11:16:33 ON 19 FEB 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:16:57 ON 19 FEB 2001

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L1        68514 S TGF BETA
L2        27819 S L1 AND 2
L3            1 S L2 AND SPERM ANTIGEN
L4          165 S L2 AND IMMUNE TOLERANCE
L5            1 S L4 AND IMPLANTATION
L6         3106 S TRANSFORMING GROWTH FACTOR BETA-2
L7            0 S L6 AND MATERNAL IMMUNE TOLERANCE
L8            2 S L6 AND FERTILITY
L9         3106 S TRANSFORMING GROWTH FACTOR.BETA.2
L10           2 S L9 AND SEMINAL PLASMA
L11          37 S L9 AND TROPHOBLAST
L12           3 S L11 AND FIBRONECTIN
L13           0 S L11 AND TROPHO ULTERONECTIN
L14           0 S L11 AND UTERONECTIN
L15           0 S L11 AND TROPHO-UTERONECTIN
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=> s l9 and immunomodulation

L16 16 L9 AND IMMUNOMODULATION

=> dup remove l16

PROCESSING COMPLETED FOR L16
L17 16 DUP REMOVE L16 (0 DUPLICATES REMOVED)

=> d l17 1-16

L17 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2001 ACS
AN 2000:82564 CAPLUS
DN 132:221258
TI Analysis of immunomodulatory activities of aqueous humor from eyes of mice
with experimental autoimmune uveitis
AU Ohta, Kouichi; Wiggert, Barbara; Yamagami, Satoru; Taylor, Andrew W.; Streilein, J. Wayne
CS Schepens Eye Research Institute and Department of Ophthalmology, Harvard Medical School, Boston, MA, 02114, USA
SO J. Immunol. (2000), 164(3), 1185-1192
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
RE.CNT 48
RE
(1) Agarwal, R; J Immunol 1999, V162, P2648 CAPLUS
(2) Apte, R; J Immunol 1998, V160, P5693 CAPLUS
(12) Gijbels, K; Mol Med 1995, V1, P795 CAPLUS
(14) Granstein, R; J Immunol 1990, V144, P3021 CAPLUS
(15) Hara, Y; J Immunol 1992, V148, P1685 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000429287 EMBASE
TI **Transforming growth factor .beta.**
2 (TGF.beta.2) produces effective pleurodesis in sheep with no systemic complications.
AU Lee Y.C.G.; Lane K.B.; Parker R.E.; Ayo D.S.; Rogers J.T.; Diters R.W.; Thompson P.J.; Light R.W.
CS Dr. Y.C.G. Lee, Department of Pulmonary Medicine, St Thomas Hospital, 4220
Harding Road, Nashville, TN 37202, United States. ycgarylee@hotmail.com
SO Thorax, (2000) 55/12 (1058-1062).
Refs: 32
ISSN: 0040-6376 CODEN: THORA7
CY United Kingdom
DT Journal; Article
FS 015 Chest Diseases, Thoracic Surgery and Tuberculosis
037 Drug Literature Index
LA English
SL English

L17 ANSWER 3 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000406101 EMBASE
TI Nitric oxide augments release of chemokines from monocytic U937 cells: Modulation by anti-inflammatory pathways.
AU Muhl H.; Chang J.-H.; Huwiler A.; Bosmann M.; Paulukat J.; Ninic R.; Nold M.; Hellmuth M.; Pfeilschifter J.

CS Dr. H. Muhl, Pharmazentrum Frankfurt, Klinikum der Johann Wolfgang Goethe,
Universitat Frankfurt am Main, Theodor-Stern-Kai 7, D-65090 Frankfurt am Main, Germany. H.Muehl@em.uni-frankfurt.de
SO Free Radical Biology and Medicine, (15 Nov 2000) 29/10 (969-980).
Refs: 73
ISSN: 0891-5849 CODEN: FRBMEH
PUI S 0891-5849(00)00389-0
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English

L17 ANSWER 4 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000076625 EMBASE
TI Human astrocytomas co-expressing Fas and Fas ligand also produce TGF.beta.2 and Bcl-2.
AU Frankel B.; Longo S.L.; Ryken T.C.
CS B. Frankel, Department of Neurosurgery, SUNY Health Science Ctr. at Syracuse, 750 East Adams St., Syracuse, NY 13210, United States. frankelb@vax.cs.hscsyr.edu
SO Journal of Neuro-Oncology, (1999) 44/3 (205-212).
Refs: 42
ISSN: 0167-594X CODEN: JNODD2
CY United States
DT Journal; Article
FS 016 Cancer
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LA English
SL English

L17 ANSWER 5 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998184687 EMBASE
TI Differential effects of IGF-1 and TGF.beta.-2 on the assembly of proteoglycans in pericellular and territorial matrix by cultured bovine articular chondrocytes.
AU Van Osch G.J.V.M.; Van den Berg W.B.; Hunziker E.B.; Hauselmann H.J.
CS G.J.V.M. Van Osch, Department of Otorhinolaryngology, University of Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, Netherlands
SO Osteoarthritis and Cartilage, (1998) 6/3 (187-195).
Refs: 35
ISSN: 1063-4584 CODEN: OSCAEO
CY United Kingdom
DT Journal; Article
FS 031 Arthritis and Rheumatism
037 Drug Literature Index
LA English
SL English

L17 ANSWER 6 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998289098 EMBASE
TI The effect of cytokine mediators on prostaglandin inhibition by human decidual cells.
AU Young Ju Kim; Jung Ja Ahn; Bock Hi Woo
CS Dr. Y.J. Kim, Dept. of Obstetrics and Gynecology, Ewha Womans University Hospital, 911-1 MokDong, Yangcheonku, Seoul 158-056, Korea, Republic of
SO American Journal of Obstetrics and Gynecology, (1998) 179/1 (146-149).
Refs: 18

ISSN: 0002-9378 CODEN: AJOGAH
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
010 Obstetrics and Gynecology
LA English
SL English

L17 ANSWER 7 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97253297 EMBASE
DN 1997253297
TI Antisense oligonucleotides specific for **transforming growth factor .beta.2** inhibit the growth of malignant mesothelioma both in vitro and in vivo.
AU Marzo A.L.; Fitzpatrick D.R.; Robinson B.W.S.; Scott B.
CS A.L. Marzo, Western Australia Univ. Dept. Med., Queen Elizabeth II Medical Centre, Verdum Street, Nedlands, WA 6008, Australia.
amarzo@uniwa.uwa.edu.au
SO Cancer Research, (1997) 57/15 (3200-3207).
Refs: 35
ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
021 Developmental Biology and Teratology
LA English
SL English

L17 ANSWER 8 OF 16 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1998:77371 SCISEARCH
GA The Genuine Article (R) Number: YQ954
TI Spectrum of immunomodulating agents in human milk
AU Goldman A S (Reprint); Chheda S; Garofalo R
CS UNIV TEXAS, MED BRANCH, DEPT PEDIAT, 301 UNIV BLVD, GALVESTON, TX 77555 (Reprint)
CYA USA
SO INTERNATIONAL JOURNAL OF PEDIATRIC HEMATOLOGY/ONCOLOGY, (MAR 1997) Vol. 4,
No. 5, pp. 491-497.
Publisher: HARWOOD ACAD PUBL GMBH, C/O STBS LTD, PO BOX 90, READING, BERKS, ENGLAND RG1 8JL.
ISSN: 1070-2903.
DT Article; Journal
FS CLIN
LA English
REC Reference Count: 71
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L17 ANSWER 9 OF 16 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:310009 BIOSIS
DN PREV199699032365
TI Alpha-fetoprotein (AFP) mediated immunoregulation is not associated with **transforming growth factor-beta 2** (TGF-beta-2.
AU Semeniuk, D. J.; Murgita, R. A.
CS Dep. Microbiol. Immunol., McGill Univ., Montreal, PQ H3A 2B4 Canada
SO FASEB Journal, (1996) Vol. 10, No. 6, pp. A1442.
Meeting Info.: Joint Meeting of the American Society for Biochemistry and Molecular Biology, the American Society for Investigative Pathology and the American Association of Immunologists New Orleans, Louisiana, USA June
2-6, 1996

ISSN: 0892-6638.
DT Conference
LA English

L17 ANSWER 10 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97017166 EMBASE
DN 1997017166
TI **Transforming growth factor-.beta.**
2-mediated regulation of C3 gene expression in monocytes.
AU Drouin S.M.; Carlino J.A.; Barnum S.R.
CS S.R. Barnum, Department of Microbiology, University of Alabama at Birmingham, 1918 University Boulevard, Birmingham, AL 35294, United States
SO Molecular Immunology, (1996) 33/13 (1025-1034).
Refs: 45
ISSN: 0161-5890 CODEN: IMCHAZ
PUI S 0161-5890(96)00071-5
CY United Kingdom
DT Journal; Article
FS 025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English

L17 ANSWER 11 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96136702 EMBASE
DN 1996136702
TI **Transforming growth factor-.beta.**
2-related-decidual suppressor factor is not related to TJ6 protein.
AU Merali F.S.; Arck P.C.; Beaman K.; Clark D.A.
CS Department of Medicine, McMaster University,Hamilton, Ont., Canada
SO American Journal of Reproductive Immunology, (1996) 35/4 (342-347).
ISSN: 8755-8920 CODEN: AAJID6
CY Denmark
DT Journal; Conference Article
FS 010 Obstetrics and Gynecology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LA English
SL English

L17 ANSWER 12 OF 16 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:111128 BIOSIS
DN PREV199799410331
TI Immunomodulatory activity of conformationally restricted peptides related to TGF-beta-2 90-99 sequence.
AU Wieczorek, Zbigniew (1); Slon, Jacek J.; Siemion, Ignacy Z.
CS (1) Inst. Immunol. Exp. Ther., Polish Acad. Sci., Czerska 12, 53-114 Wroclaw Poland
SO Archivum Immunologiae et Therapiae Experimentalis, (1996) Vol. 44, No. 4, pp. 209-214.
ISSN: 0004-069X.
DT Article
LA English

L17 ANSWER 13 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 95168099 EMBASE
DN 1995168099
TI Characterization of murine pregnancy decidua transforming growth factor .beta.. I. **Transforming growth factor .beta.2**-like molecules of unusual molecular size released

in bioactive form.
AU Clark D.A.; Flanders K.C.; Hirte H.; Dasch J.R.; Coker R.; McAnulty R.J.; Laurent G.J.
CS 1200 Main Street West,Hamilton, Ont. L8N 3Z5, Canada
SO Biology of Reproduction, (1995) 52/6 (1380-1388).
ISSN: 0006-3363 CODEN: BIREBV
CY United States
DT Journal; Article
FS 010 Obstetrics and Gynecology
021 Developmental Biology and Teratology
LA English
SL English

L17 ANSWER 14 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 95269658 EMBASE
DN 1995269658
TI Systemic administration of **transforming growth factor-.beta.2** prevents the impaired bone formation and osteopenia induced by unloading in rats.
AU Machwate M.; Zerath E.; Holy X.; Hott M.; Godet D.; Lomri A.; Marie P.J.
CS INSERM Unite 349, 6 rue Guy Patin,75010 Paris, France
SO Journal of Clinical Investigation, (1995) 96/3 (1245-1253).
ISSN: 0021-9738 CODEN: JCINAO
CY United States
DT Journal; Article
FS 031 Arthritis and Rheumatism
037 Drug Literature Index
LA English
SL English

L17 ANSWER 15 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 95025765 EMBASE
DN 1995025765
TI Multiple sclerosis. Immunomodulatory effects of human astrocytes on T cells.
AU Meinl E.; Aloisi F.; Ertl B.; Weber F.; De Waal Malefyt R.; Wekerle H.; Hohlfeld R.
CS Department of Neurology, Klinikum Grosshadern, University of Munich,D-81366 Munich, Germany
SO Brain, (1994) 117/6 (1323-1332).
ISSN: 0006-8950 CODEN: BRAIAK
CY United Kingdom
DT Journal; Article
FS 008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
LA English
SL English

L17 ANSWER 16 OF 16 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 92120279 EMBASE
DN 1992120279
TI Modulation of human IgE synthesis by transforming growth factor-.beta..
AU Chang You Wu; Brinkmann V.; Cox D.; Heusser C.; Delespesse G.
CS Canada
SO Clinical Immunology and Immunopathology, (1992) 62/3 (277-284).
ISSN: 0090-1229 CODEN: CLIIAT
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English

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=> d his

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     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 11:16:57 ON
     19 FEB 2001
L1         68514 S TGF BETA
L2         27819 S L1 AND 2
L3             1 S L2 AND SPERM ANTIGEN
L4           165 S L2 AND IMMUNE TOLERANCE
L5             1 S L4 AND IMPLANTATION
L6          3106 S TRANSFORMING GROWTH FACTOR BETA-2
L7             0 S L6 AND MATERNAL IMMUNE TOLERANCE
L8             2 S L6 AND FERTILITY
L9          3106 S TRANSFORMING GROWTH FACTOR.BETA.2
L10            2 S L9 AND SEMINAL PLASMA
L11           37 S L9 AND TROPHOBLAST
L12            3 S L11 AND FIBRONECTIN
L13            0 S L11 AND TROPHO ULTERONECTIN
L14            0 S L11 AND UTERONECTIN
L15            0 S L11 AND TROPHO-UTERONECTIN
L16           16 S L9 AND IMMUNOMODULATION
L17           16 DUP REMOVE L16 (0 DUPLICATES REMOVED)

=> s 19 and knockout

L18           19 L9 AND KNOCKOUT

=> s l18 and fertility

L19            0 L18 AND FERTILITY

=> s l18 and review

L20            0 L18 AND REVIEW

=> d l18 1-19


L18  ANSWER 1 OF 19  MEDLINE
AN   97369554     MEDLINE
DN   97369554
TI   Apoptosis in adult mouse testis induced by experimental cryptorchidism.
AU   Ohta Y; Nishikawa A; Fukazawa Y; Urushitani H; Matsuzawa A; Nishina Y;
     Iguchi T
CS   Department of Veterinary Science, Faculty of Agriculture, Tottori
     University, Japan.. ohta@agr.tottori-u.ac.jp
SO   ACTA ANATOMICA, (1996) 157 (3) 195-204.
     Journal code: 09A. ISSN: 0001-5180.
CY   Switzerland
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals
EM   199710
EW   19971004

L18  ANSWER 2 OF 19  EMBASE  COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN   2000258937  EMBASE
TI   Delayed wound healing in immunodeficient TGF-.beta.1 knockout
     mice.
AU   Crowe M.J.; Doetschman T.; Greenhalgh D.G.
CS   Dr. T. Doetschman, Department of Molecular Genetics, Biochemistry and
```

Microbiology, Univ. of Cincinnati Coll. of Med., 231 Bethesda Ave (ML 524), Cincinnati, OH 45267-0524, United States. thomas.doetschman@uc.edu
SO Journal of Investigative Dermatology, (2000) 115/1 (3-11).
Refs: 54
ISSN: 0022-202X CODEN: JIDEAE
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
013 Dermatology and Venereology
022 Human Genetics
026 Immunology, Serology and Transplantation
LA English
SL English

L18 ANSWER 3 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97245206 EMBASE
DN 1997245206
TI TGF.beta.2 **knockout** mice have multiple developmental defects that are non-overlapping with other TGF.beta. **knockout** phenotypes.
AU Sanford L.P.; Ormsby I.; Gittenberger-de Groot A.C.; Sariola H.; Friedman R.; Boivin G.P.; Cardell E.L.; Doetschman T.
CS T. Doetschman, Department of Molecular Genetics, Biochemistry and Microbiology, University of Cincinnati, Cincinnati, OH 45267, United States. thomas.doetschman@uc.edu
SO Development, (1997) 124/13 (2659-2670).
Refs: 76
ISSN: 0950-1991 CODEN: DEVPED
CY United Kingdom
DT Journal; Article
FS 001 Anatomy, Anthropology, Embryology and Histology
021 Developmental Biology and Teratology
022 Human Genetics
LA English
SL English

L18 ANSWER 4 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:487540 BIOSIS
DN PREV200000487540
TI Cardiovascular malformations in transforming growth factor-beta2 **knockout** mice relate to altered apoptosis and myocardial and endocardial cushion differentiation.
AU Bartram, U. (1); Doetschmann, T.; Speer, C. P.; Poelmann, R. E. (1); Gittenberger-de Groot, A. C. (1)
CS (1) Department of Cell Biology Neurobiology and Anatomy, University of Cincinnati, Cincinnati USA
SO European Heart Journal, (August September, 2000) Vol. 21, No. Abstract Supplement, pp. 613. print.
Meeting Info.: XXII Congress of the European Society of Cardiology Amsterdam, Netherlands August 26-30, 2000 European Society of Cardiology . ISSN: 0195-668X.
DT Conference
LA English
SL English

L18 ANSWER 5 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:63101 BIOSIS
DN PREV200000063101
TI A role for p75 neurotrophin receptor in the control of hair follicle morphogenesis.
AU Botchkareva, Natalia V.; Botchkarev, Vladimir A.; Chen, Ling-Hong; Lindner, Gerd; Paus, Ralf (1)
CS (1) Department of Dermatology, University Hospital Eppendorf, University

of Hamburg, Martinistrasse 52, D-20246, Hamburg Germany
SO Developmental Biology, (Dec. 1, 1999) Vol. 216, No. 1, pp. 135-153.
ISSN: 0012-1606.
DT Article
LA English
SL English

L18 ANSWER 6 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:245507 BIOSIS
DN PREV199900245507
TI Lack of association of transforming growth factor (TGF)-beta1 and beta2 gene polymorphisms with multiple sclerosis (MS) in Northern Ireland.
AU McDonnell, G. V.; Kirk, C. W.; Hawkins, S. A.; Graham, C. A. (1)
CS (1) Department of Medical Genetics, Belfast City Hospital Trust, Lisburn Road, Belfast, BT9 7AD UK
SO Multiple Sclerosis, (April, 1999) Vol. 5, No. 2, pp. 105-109.
ISSN: 1352-4585.
DT Article
LA English
SL English

L18 ANSWER 7 OF 19 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:388670 BIOSIS
DN PREV199799687873
TI TGF-beta-2 **knockout** mice have multiple developmental defects that are non-overlapping with other TGF-beta **knockout** phenotypes.
AU Sanford, L. Phillip; Ormsby, Llona; Gittenberger-De Groot, Adriana C.; Sariola, Hannu; Friedman, Rick; Boivin, Gregory P.; Cardell, Emmma Lou; Doetschman, Thomas (1)
CS (1) Dep. Mol. Genet. Biochem. Microbiol., Univ. Cincinnati, Cincinnati, OH
45267 USA
SO Development (Cambridge), (1997) Vol. 124, No. 13, pp. 2659-2670.
ISSN: 0950-1991.
DT Article
LA English

L18 ANSWER 8 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 2000:874978 SCISEARCH
GA The Genuine Article (R) Number: 351BR
TI Cardiovascular malformations in **transforming growth factor-beta 2 knockout** mice relate to altered apoptosis and myocardial and endocardial cushion differentiation
AU Bartram U (Reprint); Doetschmann T; Speer C P; Poelmann R E; GittenbergerdeGroot A C
CS LEIDEN UNIV, DEPT ANAT & EMBRYOL, LEIDEN, NETHERLANDS; UNIV CINCINNATI, DEPT CELL BIOL NEUROBIOL & ANAT, CINCINNATI, OH 45221; UNIV CHILDRENS HOSP, WURZBURG, GERMANY
CYA NETHERLANDS; USA; GERMANY
SO EUROPEAN HEART JOURNAL, (AUG-SEP 2000) Vol. 21, Supp. [S], pp. 3388-3388.
Publisher: W B SAUNDERS CO LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND.
ISSN: 0195-668X.
DT Conference; Journal
FS CLIN
LA English
REC Reference Count: 0

L18 ANSWER 9 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 2000:577755 SCISEARCH
GA The Genuine Article (R) Number: 337DZ

TI The expression and structure of TGF-beta 2 transcripts in rat muscles
AU Koishi K (Reprint); Dalzell K G B; McLennan I S
CS UNIV OTAGO, SCH MED SCI, DEPT ANAT & STRUCT BIOL, POB 913, DUNEDIN, NEW ZEALAND (Reprint)
CYA NEW ZEALAND
SO BIOCHIMICA ET BIOPHYSICA ACTA-GENE STRUCTURE AND EXPRESSION, (24 JUL 2000)
Vol. 1492, No. 2-3, pp. 311-319.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0167-4781.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 56
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L18 ANSWER 10 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 2000:568689 SCISEARCH
GA The Genuine Article (R) Number: 336LN
TI Delayed wound healing in immunodeficient TGF-beta 1 **knockout** mice
AU Crowe M J; Doetschman T (Reprint); Greenhalgh D G
CS UNIV CINCINNATI, COLL MED, DEPT MOL GENET BIOCHEM & MICROBIOL, 231 BETHESDA AVE ML 524, CINCINNATI, OH 45267 (Reprint); UNIV CINCINNATI, COLL MED, DEPT MOL GENET BIOCHEM & MICROBIOL, CINCINNATI, OH 45267; UNIV CINCINNATI, COLL MED, DEPT SURG, CINCINNATI, OH 45267; SHRINERS HOSP CHILDREN, CINCINNATI, OH; UNIV CALIF DAVIS, DEPT SURG, DAVIS, CA 95616
CYA USA
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, (JUL 2000) Vol. 115, No. 1, pp. 3-11.
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148.
ISSN: 0022-202X.
DT Article; Journal
FS LIFE; CLIN
LA English
REC Reference Count: 53
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L18 ANSWER 11 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1999:616726 SCISEARCH
GA The Genuine Article (R) Number: 223MH
TI Characterization of GDF-10 expression patterns and null mice
AU Zhao R B; Lawler A M; Lee S J (Reprint)
CS JOHNS HOPKINS UNIV, SCH MED, DEPT MOL BIOL & GENET, BALTIMORE, MD 21205 (Reprint); JOHNS HOPKINS UNIV, SCH MED, DEPT MOL BIOL & GENET, BALTIMORE, MD 21205; JOHNS HOPKINS UNIV, SCH MED, DEPT GYNECOL & OBSTET, BALTIMORE, MD 21205
CYA USA
SO DEVELOPMENTAL BIOLOGY, (1 AUG 1999) Vol. 212, No. 1, pp. 68-79.
Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495.
ISSN: 0012-1606.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 37
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

L18 ANSWER 12 OF 19 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 97:536201 SCISEARCH
GA The Genuine Article (R) Number: XK191

TI TGF beta 2 **knockout** mice have multiple developmental defects that are nonoverlapping with other TGF beta **knockout** phenotypes
AU Sanford L P; Ormsby I; GittenbergerdeGroot A C; Sariola H; Friedman R; Boivin G P; Cardell E L; Doetschman T (Reprint)
CS UNIV CINCINNATI, DEPT MOL GENET BIOCHEM & MICROBIOL, CINCINNATI, OH 45267 (Reprint); UNIV CINCINNATI, DEPT MOL GENET BIOCHEM & MICROBIOL, CINCINNATI, OH 45267; UNIV CINCINNATI, DEPT OTOLARYNGOL, CINCINNATI, OH 45267; UNIV CINCINNATI, DEPT PATHOL & LAB MED, CINCINNATI, OH 45267; UNIV CINCINNATI, DEPT CELL BIOL NEUROBIOL & ANAT, CINCINNATI, OH 45267; UNIV HELSINKI, INST BIOTECHNOL, HELSINKI, FINLAND; LEIDEN UNIV, DEPT ANAT, LEIDEN, NETHERLANDS
CYA USA; FINLAND; NETHERLANDS
SO DEVELOPMENT, (JUL 1997) Vol. 124, No. 13, pp. 2659-2670.
Publisher: COMPANY OF BIOLOGISTS LTD, BIDDER BUILDING CAMBRIDGE COMMERCIAL PARK COWLEY RD, CAMBRIDGE, CAMBS, ENGLAND CB4 4DL.
ISSN: 0950-1991.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 76
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L18 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 2000:521293 CAPLUS
DN 133:188394
TI Delayed wound healing in immunodeficient TGF-.beta.1 **knockout** mice
AU Crowe, Maria J.; Doetschman, Thomas; Greenhalgh, David G.
CS Department of Surgery, University of Cincinnati College of Medicine, Cincinnati, OH, 45267-0524, USA
SO J. Invest. Dermatol. (2000), 115(1), 3-11
CODEN: JIDEAE; ISSN: 0022-202X
PB Blackwell Science, Inc.
DT Journal
LA English
RE.CNT 20
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L18 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 2000:184242 CAPLUS
DN 132:304474
TI Acute hepatotoxicant exposure induces TNFR-mediated hepatic injury and cytokine/apoptotic gene expression
AU Horn, Thomas L.; O'Brien, Timothy D.; Schook, Lawrence B.; Rutherford, Mark S.
CS Toxicology Graduate Program, Department of Veterinary PathoBiology, University of Minnesota, St. Paul, MN, 55108, USA
SO Toxicol. Sci. (2000), 54(1), 262-273
CODEN: TOSCF2; ISSN: 1096-6080
PB Oxford University Press
DT Journal
LA English
RE.CNT 56
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L18 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 1999:637151 CAPLUS
DN 131:332527
TI Pathogenesis of cleft palate in TGF-.beta.3 **knockout** mice
AU Taya, Yuji; O'Kane, Sharon; Ferguson, Mark W. J.
CS Division of Cells, Immunology and Development, School of Biological Sciences, The University of Manchester, Manchester, M13 9PT, UK
SO Development (Cambridge, U. K.) (1999), 126(17), 3869-3879
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
RE.CNT 52
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L18 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 1999:318514 CAPLUS
DN 131:128920
TI Lack of association of transforming growth factor (TGF)-.beta.1 and .beta.2 gene polymorphisms with multiple sclerosis (MS) in Northern Ireland
AU McDonnell, G. V.; Kirk, C. W.; Hawkins, S. A.; Graham, C. A.
CS Northern Ireland Regional Neurology Service, Royal Victoria Hospital, Belfast, UK
SO Mult. Scler. (1999), 5(2), 105-109
CODEN: MUSCFZ; ISSN: 1352-4585
PB Stockton Press
DT Journal
LA English
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L18 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 1999:52076 CAPLUS
DN 130:262560
TI The role of TGF.beta.1 in initiating hepatic stellate cell activation in vivo
AU Hellerbrand, Claus; Stefanovic, Branko; Giordano, Frank; Burchardt, Elmar R.; Brenner, David A.
CS Departments of Medicine and Biochemistry and Biophysics, University of North Carolina, Chapel Hill, NC, 27599-7080, USA
SO J. Hepatol. (1999), 30(1), 77-87
CODEN: JOHEEC; ISSN: 0168-8278
PB Munksgaard International Publishers Ltd.
DT Journal
LA English

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L18 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 1997:462877 CAPLUS
DN 127:171823
TI TGF.beta.2 **knockout** mice have multiple developmental defects that are non-overlapping with other TGF.beta. **knockout** phenotypes
AU Sanford, L. Philip; Ormsby, Ilona; Gittenberger-de Groot, Adriana C.; Sariola, Hannu; Friedman, Rick; Boivin, Gregory P.; Cardell, Emma Lou; Doetschman, Thomas
CS Departments of Molecular Genetics, Biochemistry and Microbiology, University of Cincinnati, Cincinnati, OH, 45267, USA
SO Development (Cambridge, U. K.) (1997), 124(13), 2659-2670
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists
DT Journal
LA English

L18 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 1997:147263 CAPLUS
DN 126:210210
TI Involvement of the TNF-.alpha. system and the Fas system in the induction of apoptosis of mouse mammary glands after weaning
AU Kojima, H.; Fukazawa, Y.; Sato, T.; Enari, M.; Tomooka, Y.; Matsuzawa, A.; Ohta, Y.; Iguchi, T.
CS Graduate School of Integrated Science, Yokohama City University, Yokohama, 236, Japan
SO Apoptosis (1996), 1(3), 201-208
CODEN: APOPFN; ISSN: 1360-8185
PB Rapid Science Publishers
DT Journal
LA English

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